Neuroendocrine syndromes in gynecology

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Polycystic ovarian syndrome

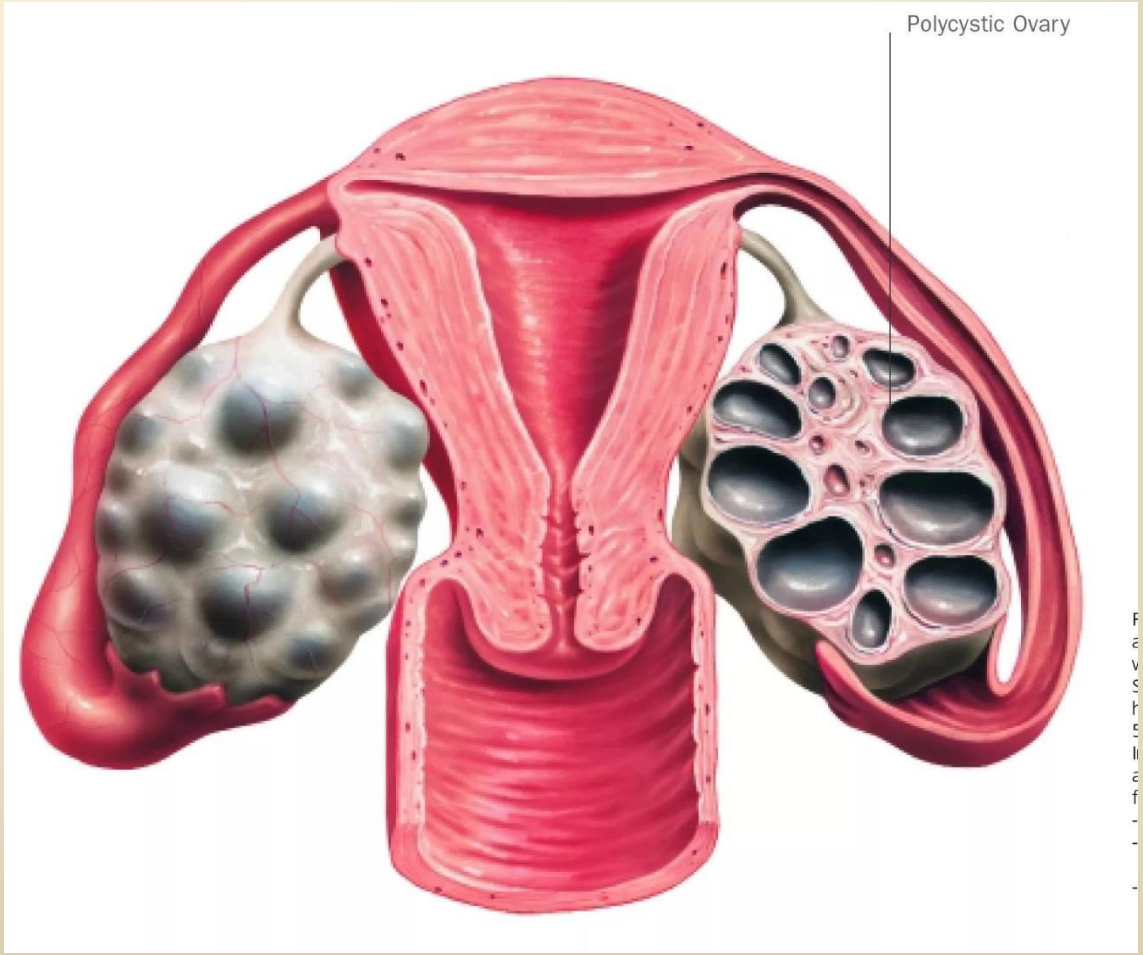
- PCOS is the most common endocrine disorder in women.
- Responsible for 80% of all cases of anovulatory subfertility.
- USS evidence of polycystic ovaries is seen in 20–30% of women.

Rotterdam criteria for diagnosing PCOS

Requires the presence **of two** out of the following variables and exclusion of other disorders:

1. **Irregular or absent ovulations (cycle >42 days).**
2. **Clinical or biochemical signs of hyperandrogenism: acne, hirsutism, alopecia.**
3. **Polycystic ovaries on pelvic USS: ≥ 12 antral follicles on one ovary, ovarian volume >10mL.**

Polycystic ovarian syndrome

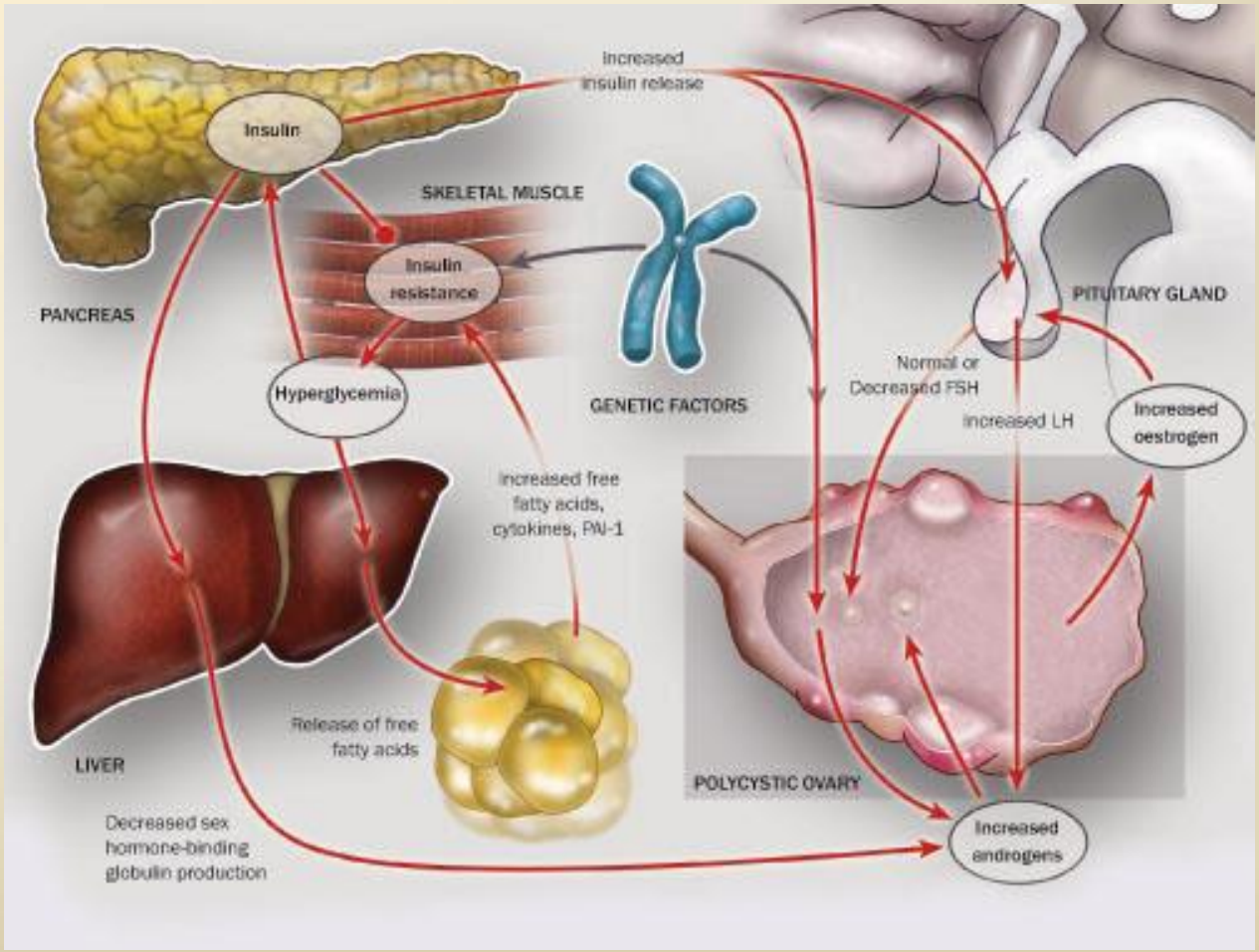


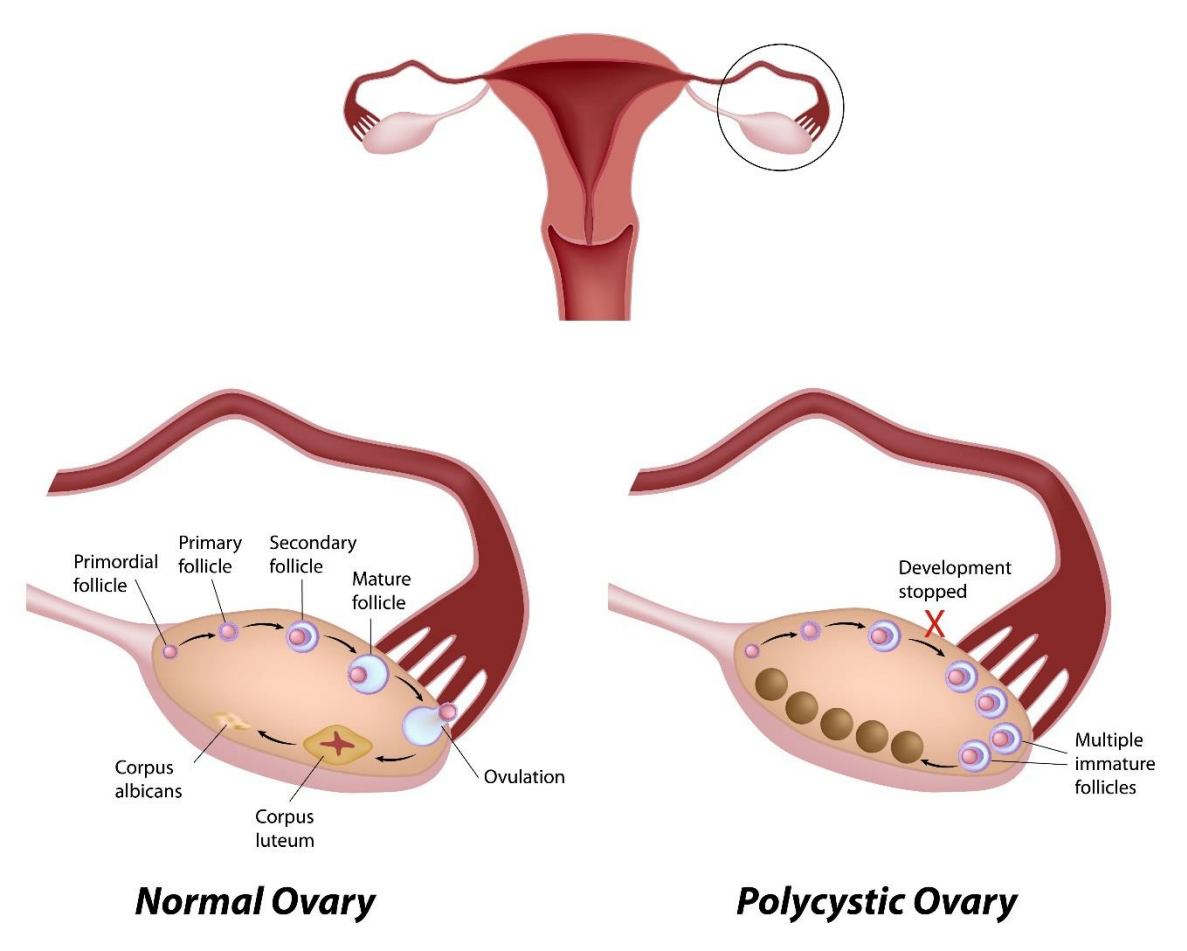
PCOS

- The pathogenesis of PCOS is not fully known.
- There is hypersecretion of LH in ~60% of PCOS patients (LH stimulates androgen secretion from ovarian thecal cells).
- Elevated LH:FSH ratio is often seen.

The following factors have been implicated:

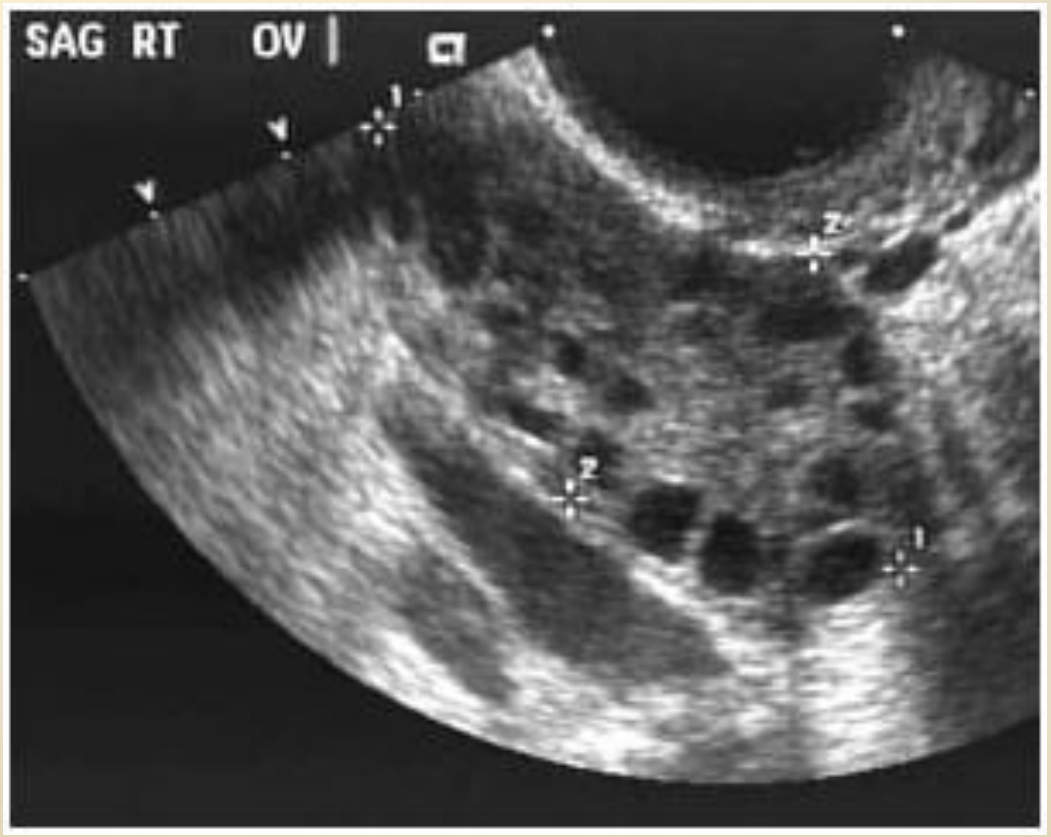
- **Genetic** (familial clustering).
- **Insulin resistance** with compensatory hyperinsulinaemia (defect on insulin receptor).
- **Hyperandrogenism** (elevated ovarian androgen secretion).
- **Obesity**: BMI >30 in 35–60% of women with PCOS, central obesity worsens insulin resistance.


Increased
insulin release
Insulin
SKELETAL MUSCLE
Insulin
resistance
PANCREAS
PITUITARY GLAND
Normal or
Decreased FSH
Hyperglycemia
GENETIC FACTORS
Increased LH
Increased
oestrogen
Increased free
fatty acids,
cytokines, PAI-1
Release of free
fatty acids
LIVER
POLYCYSTIC OVARY
Decreased sex
hormone-binding
globulin production
Increased
androgens


Primordial follicle
Primary follicle
Secondary follicle
Mature follicle
Ovulation
Corpus albicans
Corpus luteum
Normal Ovary
Development stopped
X
Multiple immature follicles
Polycystic Ovary

Investigations

- Basal (day 2–5): LH, FSH, testosterone.
- Pelvic USS.


SAG RT OV

Long-term health consequences of PCOS

- Obesity, insulin resistance, and metabolic abnormalities including dyslipidaemia are all risk factors for ischaemic heart disease, type II diabetes.
- Pregnant women with PCOS are at increased risk of gestational diabetes.
- Long periods of amenorrhoea, with unopposed oestrogen, are a risk factor for endometrial hyperplasia and, if untreated, endometrial carcinoma.

Polycystic ovarian syndrome: management

- **Lifestyle modification (overweight women)**
- Even a modest weight loss (5%) can improve symptoms. Moreover, weight loss through exercise and diet has been proven effective in restoring ovulatory cycles and achieving pregnancy.

Polycystic ovarian syndrome: management

- **Improving menstrual regularity**
- Weight loss
- COCP – 3 month
- Metformin 1000-1200 mg/day, 3- 6 month.

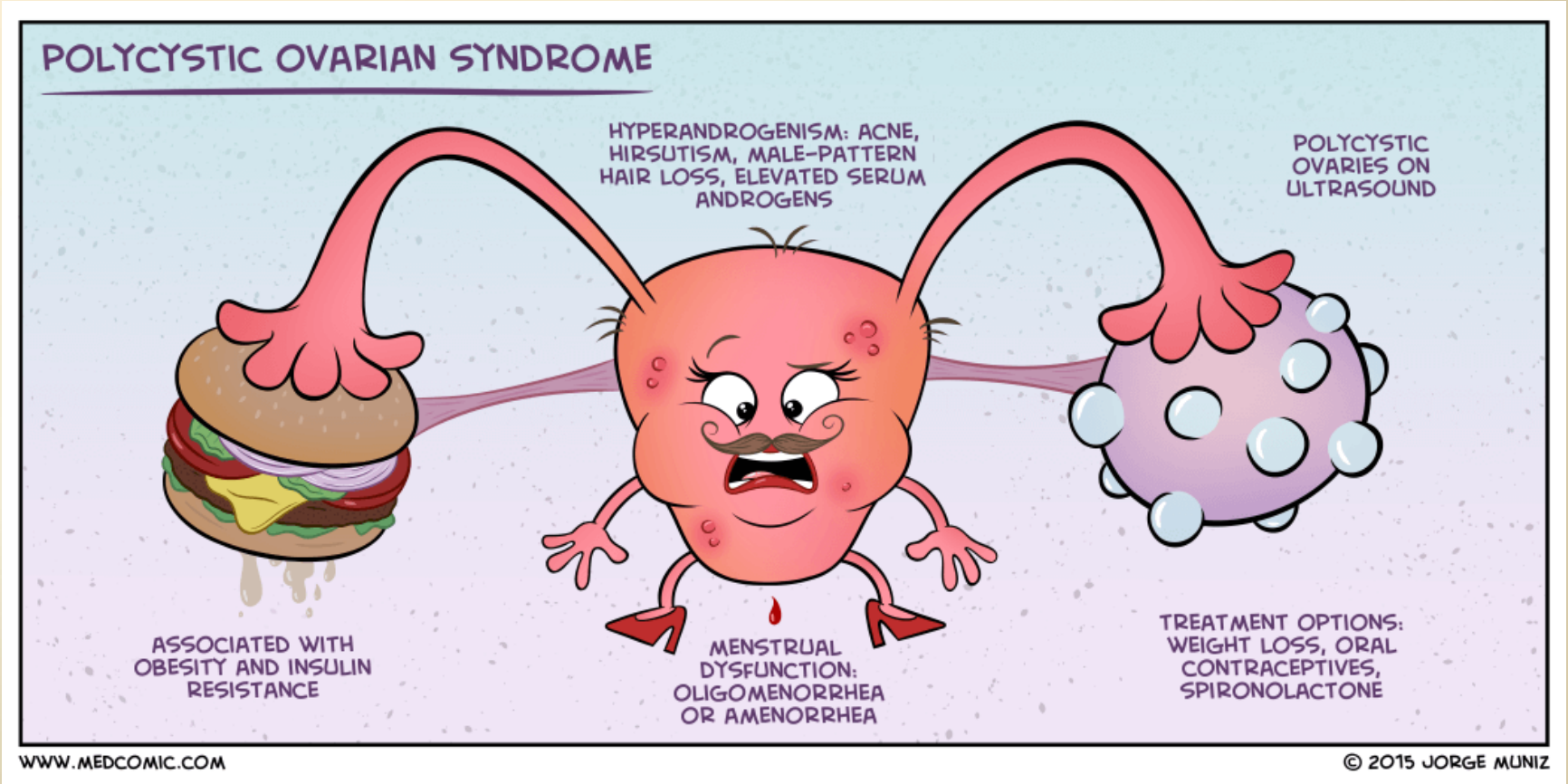
Metformin combined with ovulation induction with clomifene citrate also increases ovulation and pregnancy rates

Controlling symptoms of hyperandrogenism

- Cosmetic (depilatory cream, electrolysis, shaving).
- Antiandrogen such as spironolactone can be used to help with acne and hirsutism.
- COCP: reduces serum androgen levels by increasing SHBG levels.

Subfertility

- **Weight loss** alone may achieve spontaneous ovulation.
- **Ovulation induction** with antioestrogens or gonadotrophins.
- **Laparoscopic ovarian diathermy**.
- **IVF** if ovulation cannot be achieved or does not succeed in pregnancy.
- Women with PCOS who undergo IVF are at increased risk of ovarian hyperstimulation syndrome.


POLYCYSTIC OVARIAN SYNDROME
HYPERANDROGENISM: ACNE, HIRSUTISM, MALE-PATTERN HAIR LOSS, ELEVATED SERUM ANDROGENS
POLYCYSTIC OVARIES ON ULTRASOUND
ASSOCIATED WITH OBESITY AND INSULIN RESISTANCE
MENSTRUAL DYSFUNCTION: OLIGOMENORRHEA OR AMENORRHEA
TREATMENT OPTIONS: WEIGHT LOSS, ORAL CONTRACEPTIVES, SPIRONOLACTONE
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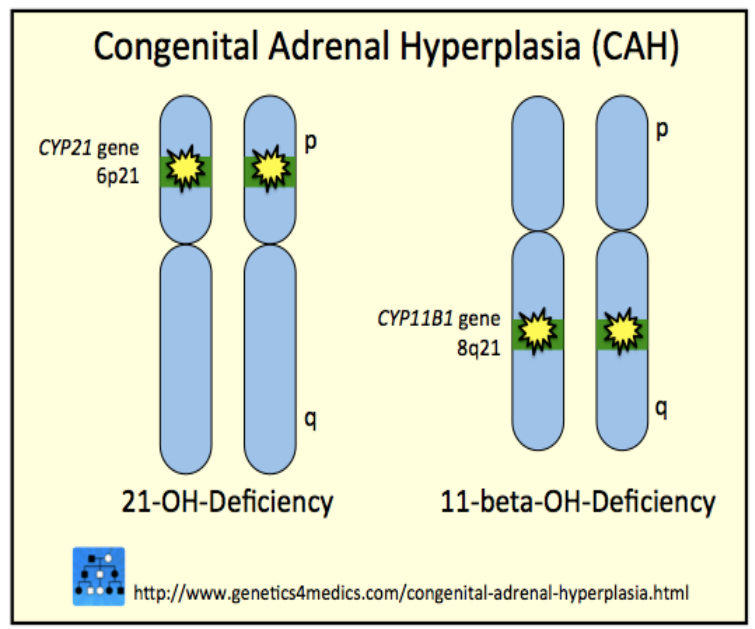
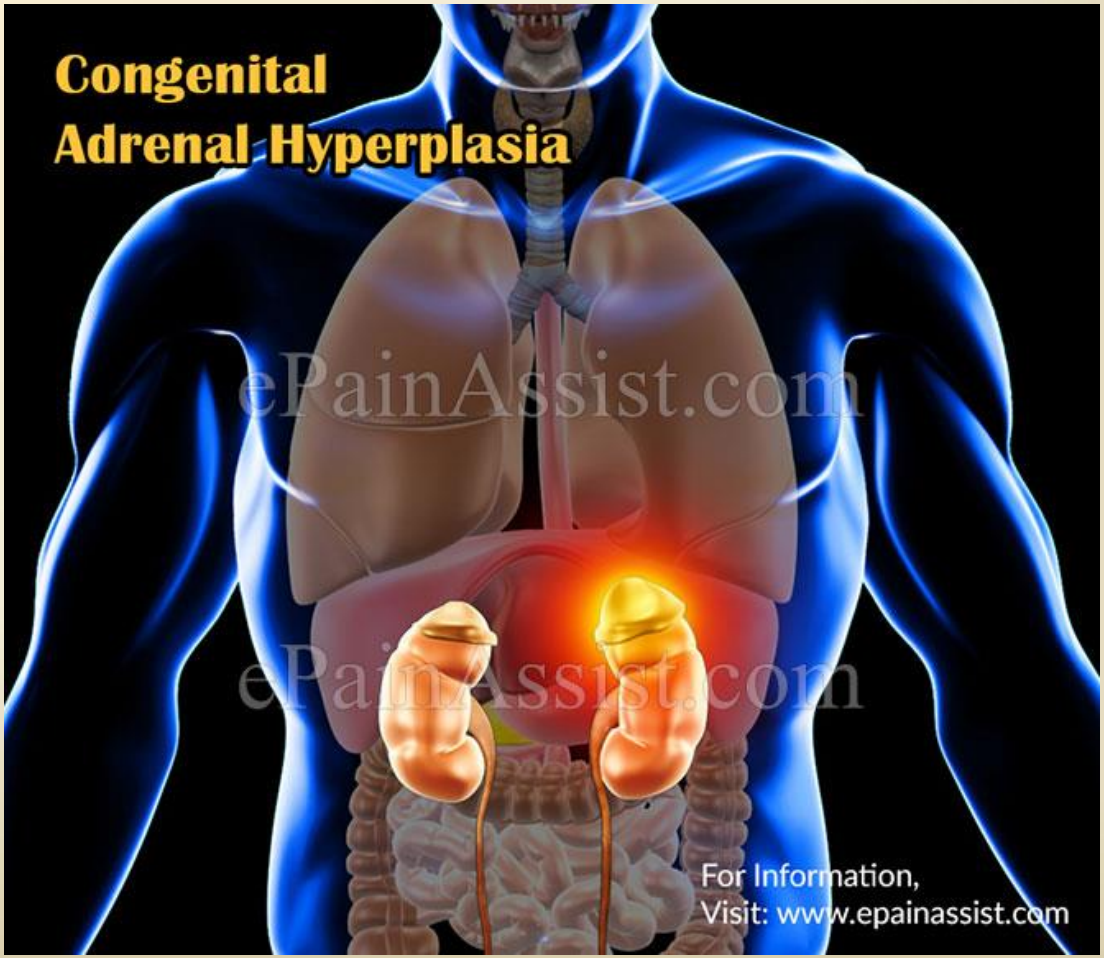
CONGENITAL ADRENAL HYPERPLASIA

- Etiology - autosomal recessive disorder.
- It is due to inborn error of adrenal steroid metabolism, commonly due to 21-hydroxylase (95%) deficiency.



CONGENITAL ADRENAL HYPERPLASIA

- There is lack of cortisol production resulting in excess of ACTH production from the pituitary.
- ACTH in turn, stimulates the adrenal to produce excess androgens with virilization of female offspring.
- Associated aldosterone deficiency may lead to excess salt depletion.
- The girls are potentially fertile.


Congenital
Adrenal Hyperplasia
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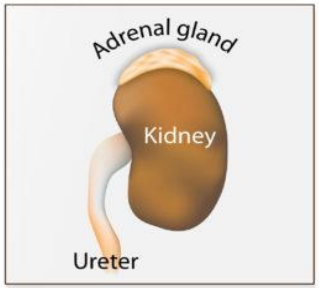
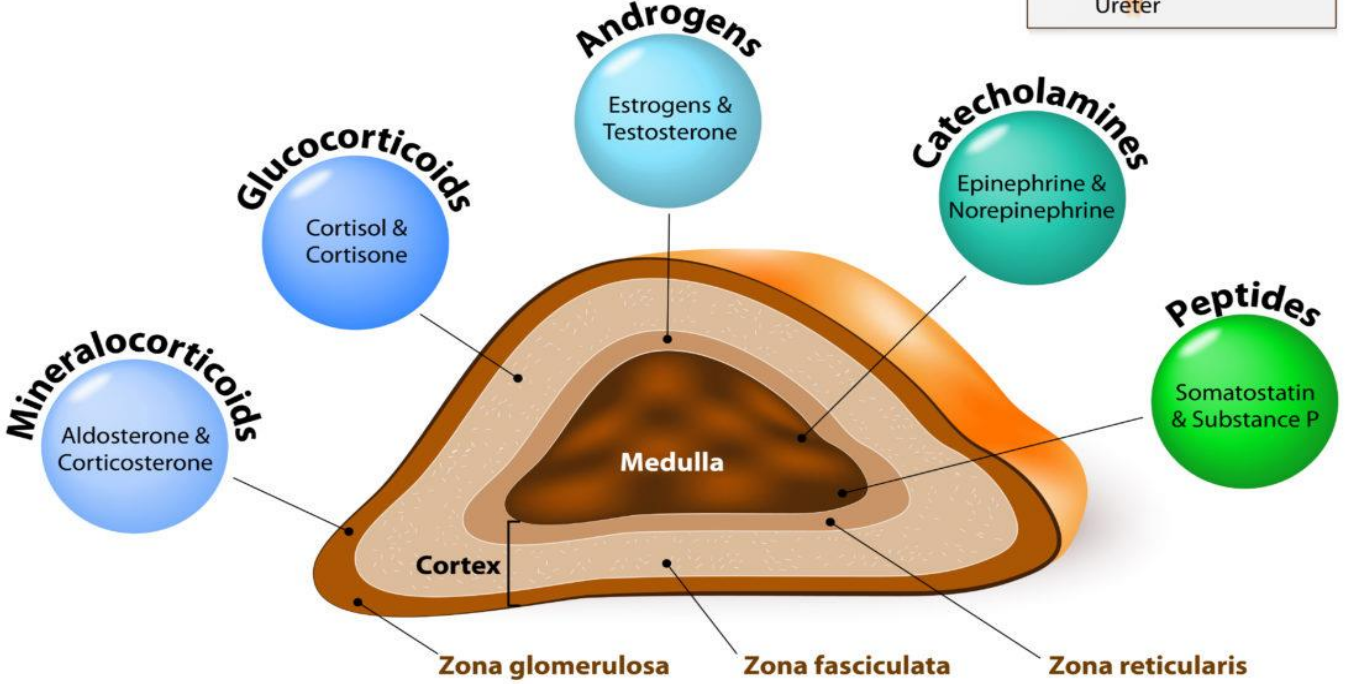
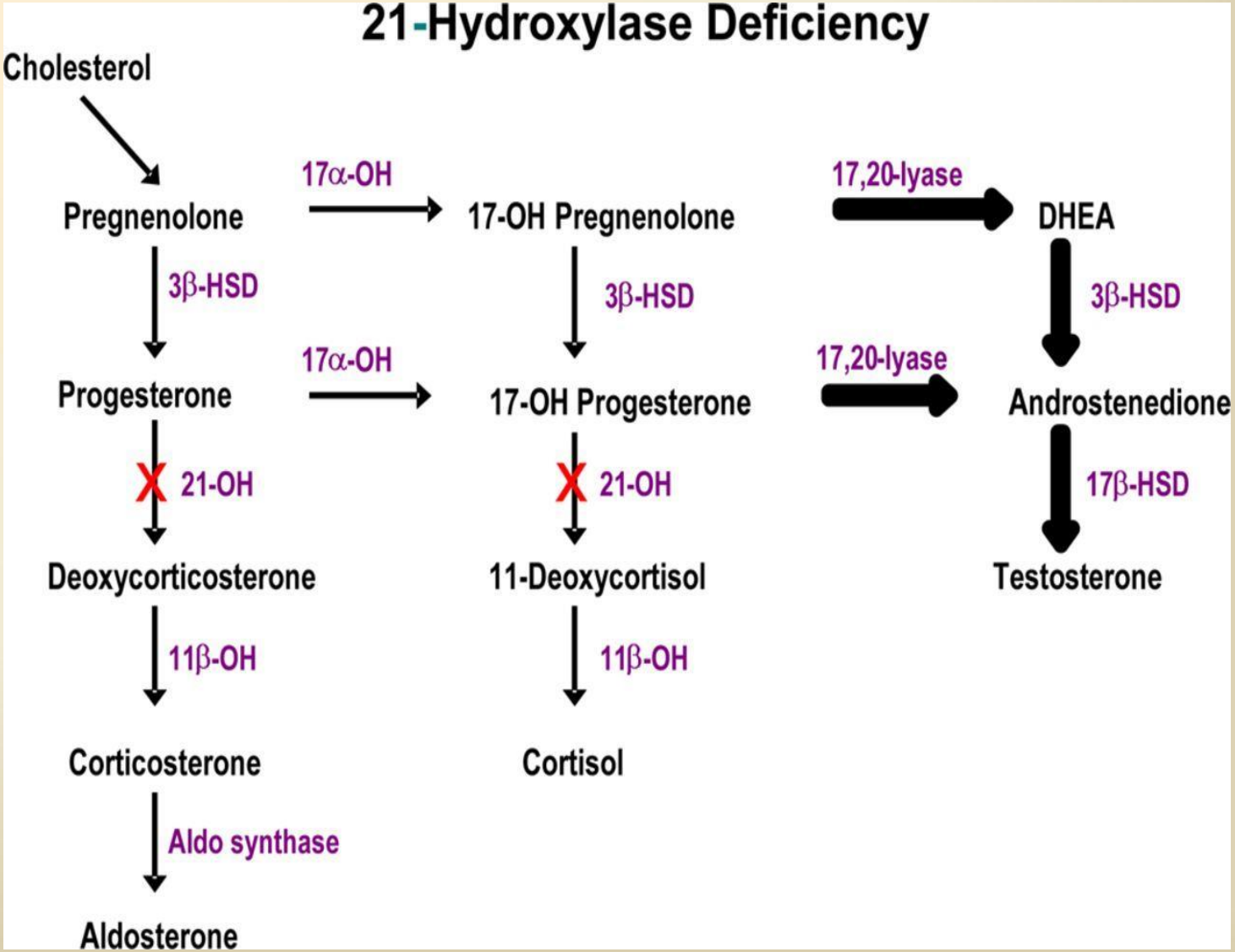
ADRENAL GLAND

(hormones)






21-Hydroxylase Deficiency
Cholesterol
Pregnenolone
17α-OH
17-OH Pregnenolone
17,20-lyase
DHEA
3β-HSD
3β-HSD
3β-HSD
Progesterone
17α-OH
17-OH Progesterone
17,20-lyase
Androstenedione
21-OH
21-OH
17β-HSD
Deoxycorticosterone
11-Deoxycortisol
Testosterone
11β-OH
11β-OH
Corticosterone
Cortisol
Aldo synthase
Aldosterone

Clinical presentation

- **Ambiguity of sex**
- **Hirsutism and amenorrhea**

Mixed gonadal dysgenesis: with ambiguous genitalia & a unilateral palpable gonad on the Rt. Side.

Diagnosis at birth

- The suspected anatomic abnormalities include:
- An enlarged clitoris
- Associated metabolic abnormality—salt wasting (hyponatremia, hyperkalemia) and hypotension may be present.
- Fusion of the labia minora.

Investigations

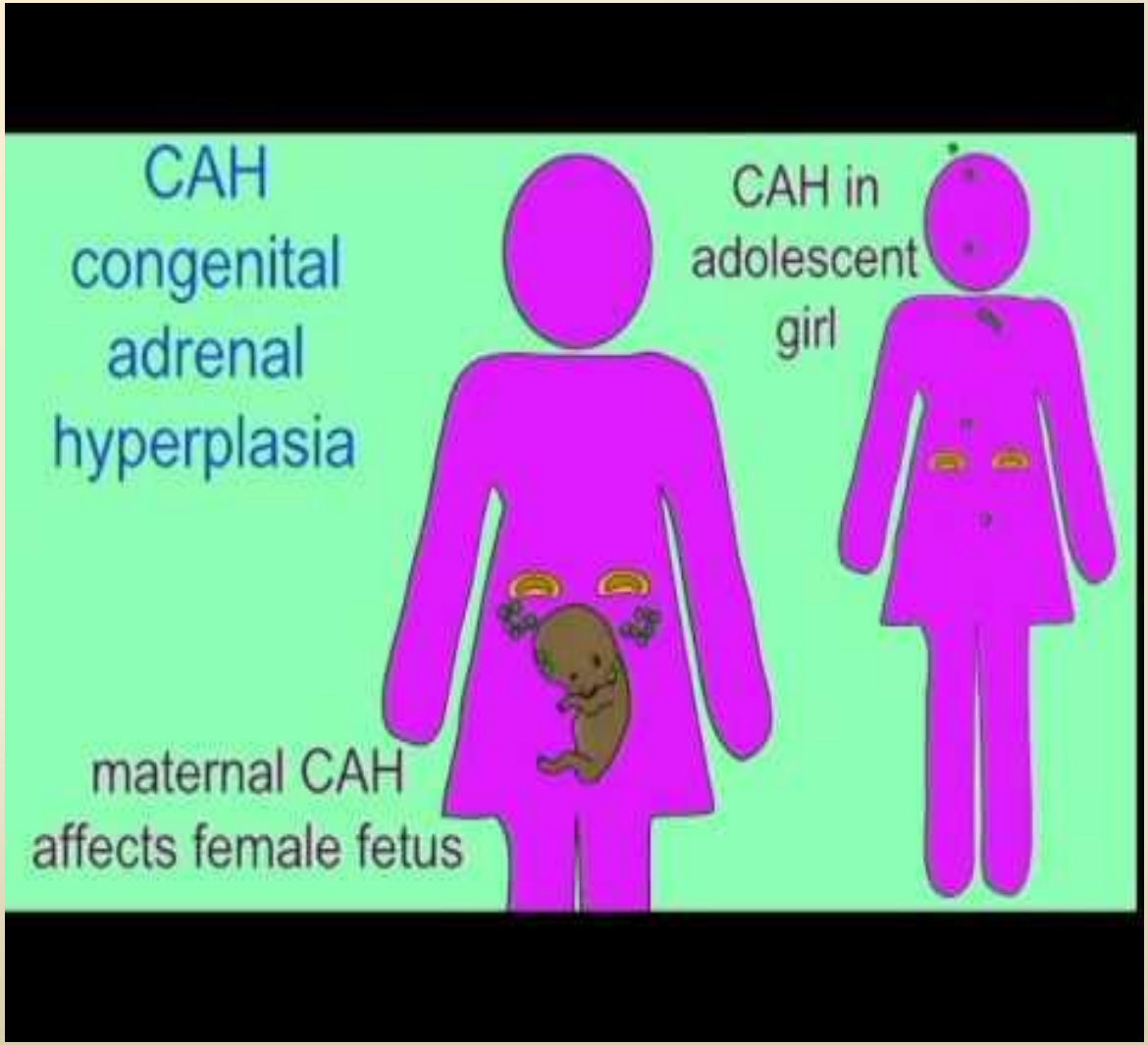
- Sonographic evaluation of internal genitalia shows presence of uterus. The gonads are ovaries.
- Karyotype is 46, XX.
- Serum estimation – 17 hydroxy-progesterone (17 OHP) is elevated.
- Electrolyte values are estimated to check the possibility of their depletion and producing “salt loosing syndrome” (sodium and chloride— low, potassium—raised).

Management of CAH

- A multidisciplinary approach by paediatric urologists, endocrinologists, psychologists, and gynaecologists is required.
- Treatment requires **replacement glucocorticoid** to suppress ACTH and excess androgen production (dexamethasone, hydrocortisone, or prednisolone).

Management of CAH

- **In pregnancy**: prenatal diagnosis is available if a previous child has CAH: dexamethasone is started with a positive pregnancy test (it crosses the placenta and suppresses the fetal adrenal)
- If US then shows the fetus is male or negative for the gene mutation, it can be stopped.


CAH
congenital
adrenal
hyperplasia
CAH in
adolescent
girl
maternal CAH
affects female fetus

Menopause: overview

- The menopause is the cessation of the menstrual cycle and is caused by ovarian failure leading to oestrogen deficiency.
- All women will go through the menopause in the average age is 52yrs.

Menopause: overview

- Worldwide life expectancy is increasing and women live longer than men.
- A woman's average life expectancy in the UK is currently 81yrs (RB – 70). Thus, UK women can expect more than 30yrs of post-menopausal life, belorussian – more than 20.
- This population expansion will lead to an increasing importance of the health problems that affect post-menopausal women.

Perimenopause

Menopause

Post-Menopause

Definitions

- **Menopause** is the permanent cessation of menstruation that results from loss of ovarian follicular activity.
- Natural menopause is recognized to have occurred after **12 months of amenorrhoea** for which no other obvious pathological or physiological cause is present.

Definitions

- **Perimenopause** includes the period beginning with the first clinical, biological, and endocrinological features of the approaching menopause, such as vasomotor symptoms and menstrual irregularity, and ends 12mths after the last menstrual period.

Definitions

- **Post-menopause** should be defined from the final menstrual period regardless of whether the menopause was induced or spontaneous.
- **Climacteric** is the phase encompassing the transition from the reproductive state to the non-reproductive state.
- The menopause itself thus is a specific event that occurs during the climacteric, just as the menarche is a specific event that occurs during puberty.

Pathophysiology

- **Reduced pool of follicles -** the oestrogen levels start to fall. Oestrogen levels drop due to reduction in follicle.
- This is associated with an increase in the production of FSH and a decrease in the level of inhibin produced by the follicles.
- The FSH rises.

Pathophysiology

- Permanent cessation of progesterone production can lead to endometrial proliferation and hyperplasia.
- AMH, a peptide secreted by the granulosa cells from the pre-antral and antral follicles, has recently been shown to be a marker of ovarian reserve independently of FSH.
- AMH level decreases as the number of follicles decline.

Symptoms

- **Acute**
- Hot flushes, 70%
- Night sweats, 70%
- Insomnia
- Anxiety
- Memory loss
- Poor concentration
- Mood changes
- **Intermediate**: Urethral syndrome, Vaginal atrophy
- **Late:** Osteoporosis

Hot flushes

- **Vasomotor symptoms**
- Hot flushes and night sweats are the commonest symptoms of the menopause.
- The hot flush, although it may characteristically start over the face or neck area, involves the whole body and is often followed by intense sweating.
- Hot flushes occur in 70% of Caucasian and Afro-Caribbean women but are less common in Japanese and Chinese women; this may be cultural or possibly due to a high isoflavone diet.

CNS systems

- Oestrogen and progesterone receptors are co-located in the CNS.
- In these areas they mediate genomic effects, e.g. limbic system functions emotion and behaviour.
- The depression that is seen at the menopause is partly due to serotonin and noradrenaline deficit.
- Oestrogen increases the levels of these neurotransmitters.

Psychological symptoms

- Psychological symptoms associated with the menopause include:
- Depressed mood.
- Anxiety.
- Irritability and mood swings.
- Lethargy and lack of energy.

Menopause: long-term consequences

- **Osteoporosis**
- Osteoporosis affects 1 in 3 women and 1 in 12 men
- Osteoporosis becomes a serious health threat for aging postmenopausal women by predisposing them to an increased risk of fracture.
- Osteoporotic fractures are associated with morbidity and mortality in postmenopausal women, especially older women.

Menopause: long-term consequences

- **Cardiovascular disease**
- Cardiovascular disease (CVD) is the most common cause of death in women over 60.
- Oophorectomized women are at 2–3-fold higher risk of coronary heart disease (CrHD) than age-matched pre-menopausal women.

Menopause: long-term consequences

- **Urogenital atrophy**
- Oestrogen receptors and progesterone receptors are present in the vagina, urethra, bladder, and pelvic floor musculature.
- Oestrogen deficiency after menopause causes atrophic changes within the urogenital tract and is associated with urinary symptoms, such as frequency, urgency, nocturia, incontinence, and recurrent infection.
- These symptoms may coexist with those of vaginal atrophy, including dyspareunia, itching, burning, and dryness.

Investigations

- **FSH** only helpful if diagnosis is in doubt, such as below age 40 and levels in menopausal range (>30IU/L).
- Luteinizing hormone, oestradiol, and progesterone are of no value in the diagnosis of ovarian failure.
- BMD. Bone strength is dependent on many qualities of bone, of which bone mineral density (BMD) is the most commonly measured. Expressed as grams of mineral per area or volume.

Premature menopause

- Premature menopause should be defined as menopause that occurs at an age below the mean estimate for the reference population.
- The age of 40yrs is used frequently as an arbitrary limit below which the menopause is said to be premature.
- It affects 1% of women younger than 40yrs and 0.1% of those under 30yrs.

Premature menopause

- Iatrogenic: Radiation therapy, Chemotherapy (cyclo- phosphamide), Surgery.
- Clinical features: the same.
- Treatment: HRT, if not contraindicated.

International Menopause Society (IMS) recommendations (2011)

- HRT should be prescribed with a clear indication (significant symptoms or physical effects of oestrogen deficiency).
- Women can have the option of HRT as long as they have a symptomatic benefit and are aware of the risks.
- The risks and benefits have to be clearly explained.
- The lowest effective dose should be used.
- Women taking HRT should be assessed at least annually (a physical examination, laboratory and imaging investigations).

HRT preparations

- **Oestrogens** are effective at relieving menopausal symptoms.
- For all women who have **not had a hysterectomy**, a **progestogen** should be added for at least 12 days of each month to prevent endometrial hyperplasia and carcinoma.
- In order to decrease the potential risks associated with HRT, the preference should be for natural hormones, i.e. oestradiol and progesterone.

HRT preparations

- The routes of administration of the oestrogen can be:
- Oral
- Patches
- Gel

HRT preparations

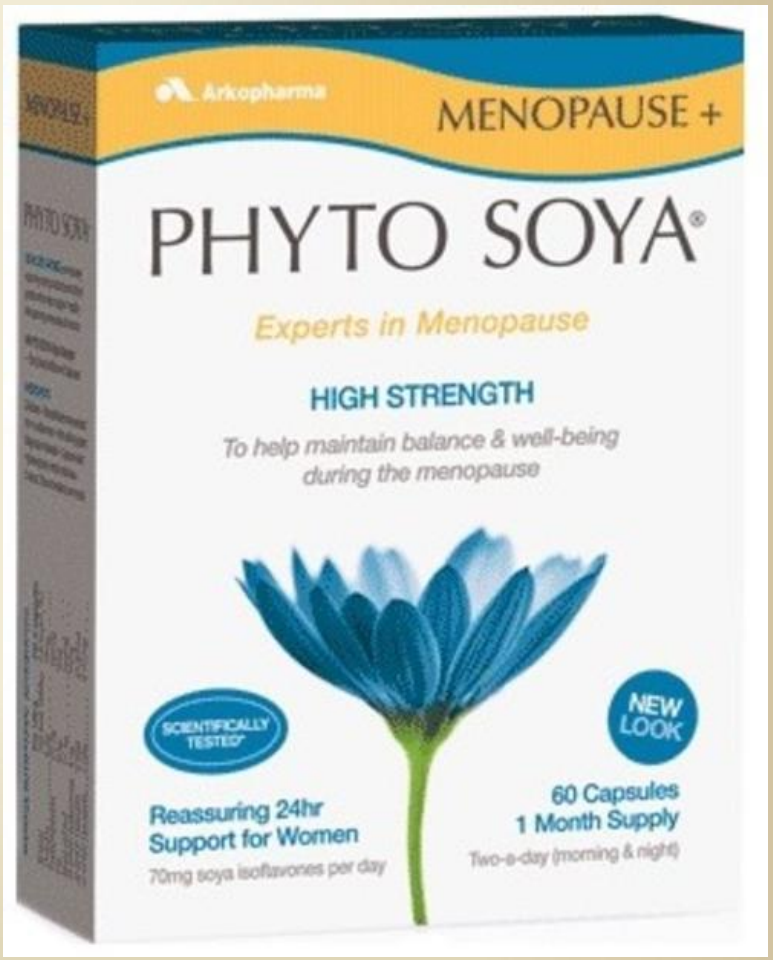
- **Oral regimens.** Oestrogen is given continuously, with progestogen added for at least 12 days per cycle, in women with an intact uterus. Oral regimens do, however, deliver a high level of oestrogen to the liver with increased risk of thrombotic events.
- **Transdermal regimens.** No increased risk of venous thrombosis with use of transdermal oestrogens.
- **Vaginal preparations.** Vaginal oestrogen cream is indicated for use for atrophic vaginitis. They do not prevent osteoporosis. Long-term use by the vaginal route is not associated with endometrial hyperplasia.

Side effects and complications of HRT

- **Venous thrombosis.** There is a very small increased risk of venous thrombosis in women on HRT who do not have a previous history of venous thrombosis.The first 12 months of treatment are associated with the highest risk.
- **Breast disease.** The increased risk of breast cancer associated with HRT is relatively low.

Alternative treatment

- Soy-derived isoflavones have been shown to have some clinical benefits in the treatment of hot flushes.
- Selective oestrogen receptors modulators (SERMs) are effective in the prevention of bone loss and reduce the incidence of breast cancer. They may increase hot flushes slightly.



Premenstrual syndrome

- Most women of reproductive age notice symptoms/bodily changes in the days/weeks leading up to their periods.
- These changes resolve or ↓ significantly during the period and are termed **premenstrual tension (PMT),** or **premenstrual syndrome (PMS)** if they occur on a regular basis and are severe enough to interfere with quality of life.

Etiology

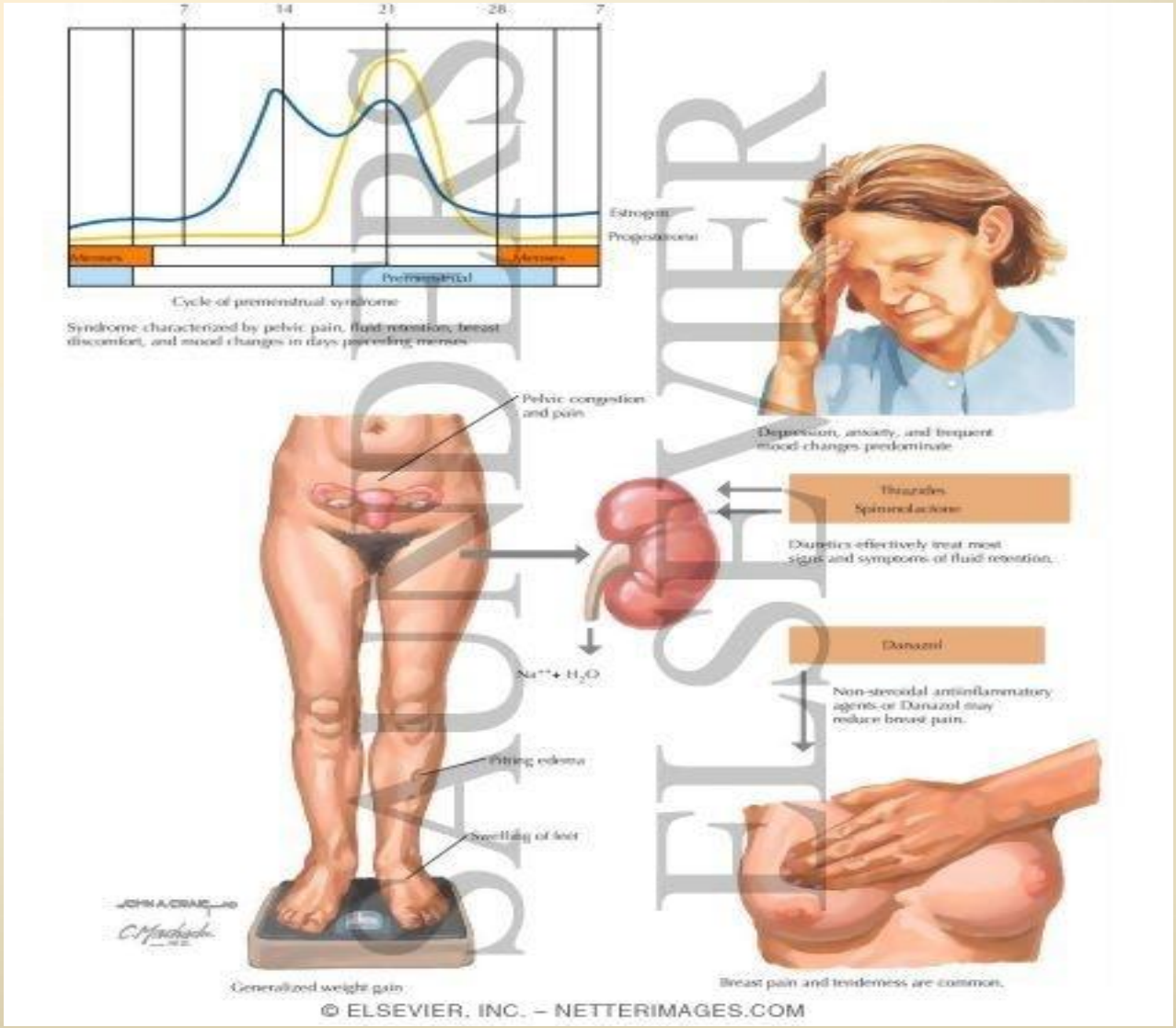
- Multiple aetiologies, but **cyclical ovarian activity** is likely to be the central component
- ovarian ‘trigger’, such as ovulation, may initiate a cascade of events

Diagnosis

- A detailed history can suggest a diagnosis of PMS, but only prospective assessment with a symptom diary can establish its true nature.
- Moderate/severe PMS involves disruption of work and interpersonal relationships, or interference with normal activities.
- It is important to exclude organic disease and significant psychiatric illness.

DSM-IV criteria for premenstrual dysphoric disorder

- At least 5 symptoms present for most of the late luteal phase with remission within a few days of onset of menses and absence of symptoms in the week post menses. At least one symptom must be from the following first four:
- **Markedly depressed mood**
- **Marked anxiety**
- **Marked affective lability (e.g. feeling suddenly sad or tearful).**
- **Persistent and marked anger/irritability/increased conflicts.**
- Decreased interest in usual activities (school, friends, hobbies).
- Subjective sense of difficulty in concentrating.
- Lethargy, easy fatiguability/lack of energy.
- Marked change in appetite, overeating, or specifi c food cravings.
- Hypersomnia or insomnia.
- Subjective sense of being overwhelmed or out of control.
- Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sense of ‘bloating’, weight gain.


7
14
21
28
7
Estrogen
Progesterone
Menses
Menses
Premenstrual
Cycle of premenstrual syndrome
Syndrome characterized by pelvic pain, fluid retention, breast discomfort, and mood changes in days preceding menses
Pelvic congestion and pain
Depression, anxiety, and frequent mood changes predominate
Thiazides
Spironolactone
Diuretics effectively treat most signs and symptoms of fluid retention.
$Na^{++} + H_2O$
Danazol
Non-steroidal antiinflammatory agents or Danazol may reduce breast pain.
Pitting edema
Swelling of feet
Generalized weight gain
Breast pain and tenderness are common.
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Premenstrual syndrome: management

- **Progesterone and progestogens**
- A meta-analysis suggests **no benefit** of progesterone pessaries, suppositories, depot injections, or oral formulations.

Ovulation suppression agents

- COCP: appears useful for some women.
- However, some women have PMS-type progestagenic side effects or symptoms during the pill-free interval.
- **Yasmin® (YAZ)** contains drospirenone with a better side effect profile, and newer pills with a 2–4-day break or with no pill-free interval may be more therapeutic.
- **Danazol**: 4 RCTs report benefit for PMS, but there are significant masculinizing side effects.
- **GnRH analogues** : are of proven benefit for moderate to severe PMS

Non-hormonal

- **Antidepressants**: tricyclics and anxiolytics have benefits for selected patients as indicated in at least 9 studies (UK).
- **Vitamin B.**
- **Chaste tree berry (Vitex agnus-castus).**

Hyperprolactinemia

- Prolactin is a protein hormone, is synthesized and released primarily b the lactotrophs located in the anterior pituitary gland.
- Prolactin secretion from the anterior pituitary is under the inhibitory control of dopamine.
- Hyperprolactinemia is commonly due to pituitary adenomas (microadenoma or macroadenoma).
- Normal plasma level of prolactin is 1–20 ng/mL.

CAUSES OF HYPERPROLACTINEMIA

- **Physiological**. Stress and exercise ,pregnancy.
- **Drugs**. Phenothiazines , Metoclopramide, Antidepressants
- **Hypothalamus and pituitary** Craniopharyngioma , pituitary adenomas (Prolactinomas).

Hyperprolactinemia

- Prolactin inhibits GnRH pulse secretion, gonadotropin levels are suppressed.
- Hyperprolactinemia inhibits ovarian steroidogenesis, causes secondary **amenorrhea** in about 30% of women.
- There is **anovulatio**n and hypogonodotropic hypagonadism.

Diagnosis

- Prolactin level is more than 100 ng/mL is often associated with prolactinoma.
- Computerized tomography (CT) is helpful for macroadenomas.

Hyperprolactinemia: treatment

- Medical: **Bromocriptine** - a dopamine agoinst is the drug first choice.
- Common side effects are: nausea, vomiting, headache.
- **Cabergoline** is a selective dopamine agonist. It has less side effects, greater potency and longer duration of action.
- Prolactin levels usually decrease within 2–3 weeks of treatment. Menses, ovulation and fertility return when prolactin level returns to normal.

Hyperprolactinemia: treatment

- Surgery is considered when there is failure of medical therapy.
- Transnasal — trans-sphenoidal adenectomy is done.

SHEEHAN'S SYNDROME

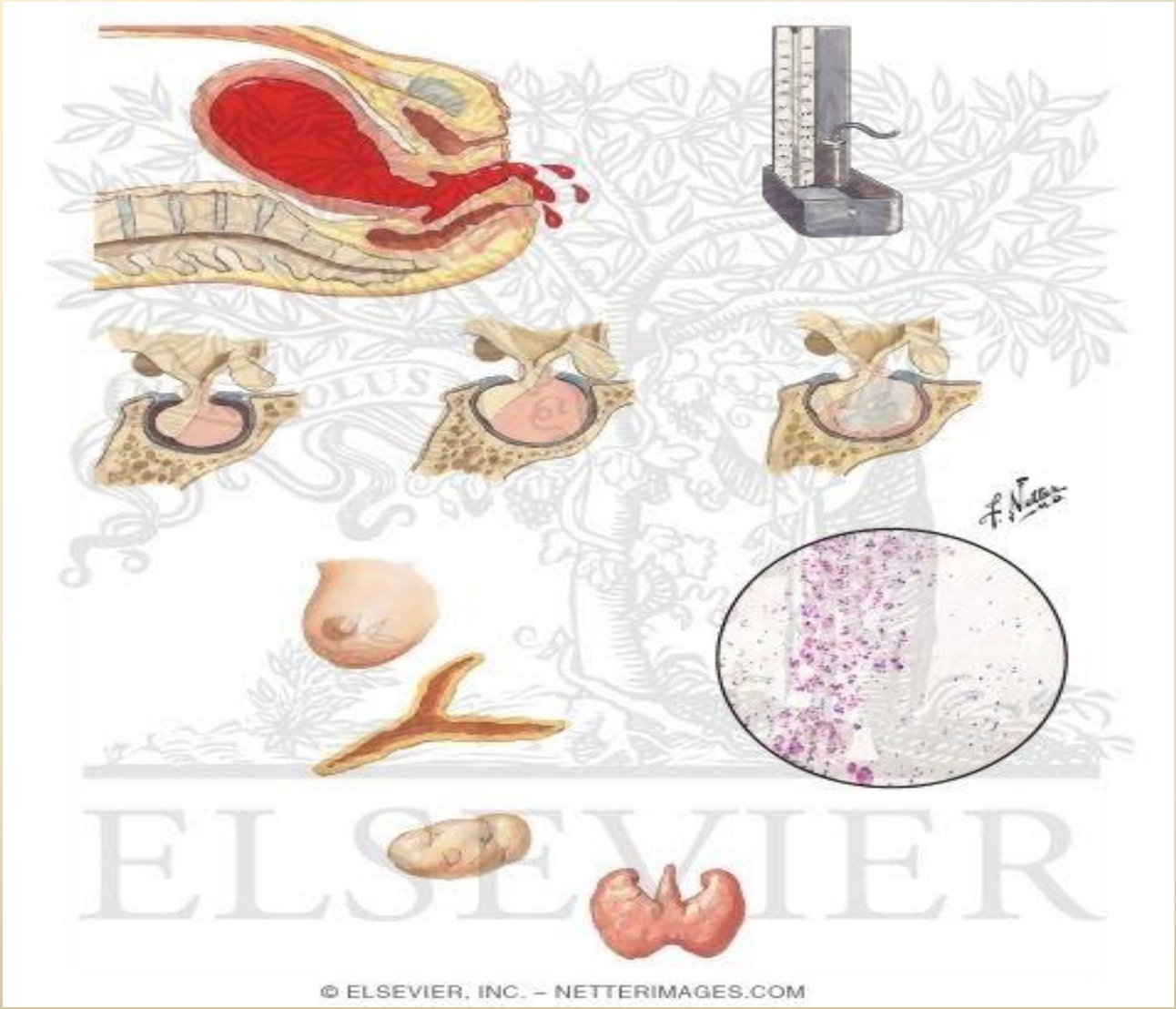
- There is history of severe postpartum hemorrhage, shock or severe infection.
- Depending upon the degree of anterior pituitary necrosis, the features vary.

SHEEHAN'S SYNDROME

- The common manifestations are failing lactation
- loss of pubic and axillary hair
- lethargy,
- hypotension,
- secondary amenorrhea
- atrophy of the breasts and genitalia.
- The syndrome may develop slowly over 8–10 years time.

SHEEHAN'S SYNDROME

- Gonadotropin level is low, so also T3, T4 and cortisol.
- Gonadotropins (FSH and LH), TSH and ACTH ↓.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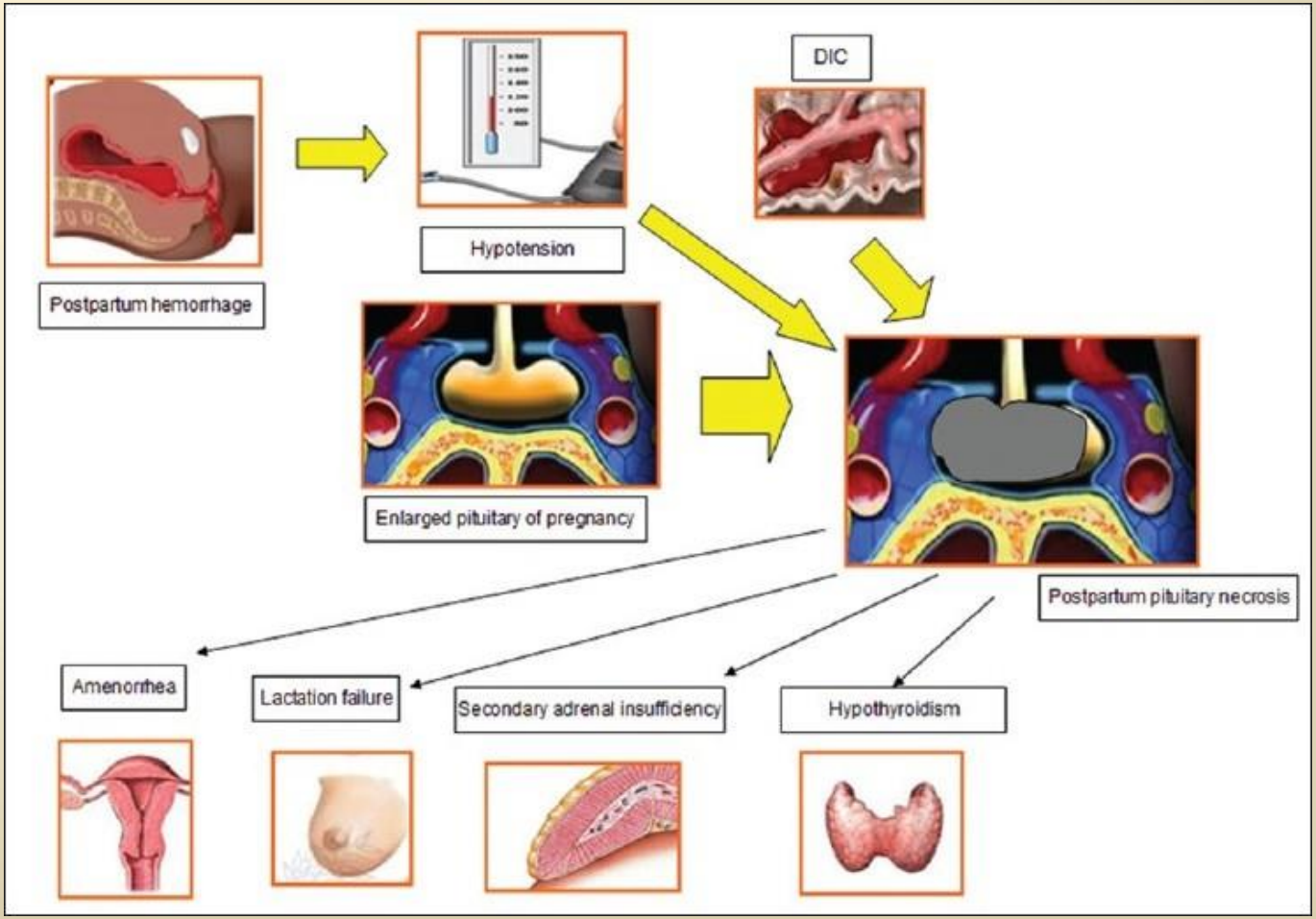
DIC
Hypotension
Postpartum hemorrhage
Enlarged pituitary of pregnancy
Postpartum pituitary necrosis
Amenorrhea
Lactation failure
Secondary adrenal insufficiency
Hypothyroidism

Management

- Replacement therapy with appropriate hormones including corticosteroid and thyroid are needed.