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БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА АКУШЕРСТВА И ГИНЕКОЛОГИИ С КУРСОМ
ПОВЫШЕНИЯ КВАЛИФИКАЦИИ И ПЕРЕПОДГОТОВКИ

Л. Ф. Можейко, С. А. Павлюкова, Е. Н. Кириллова

НЕЙРОЭНДОКРИННЫЕ СИНДРОМЫ В ГИНЕКОЛОГИИ

NEUROENDOCRINE SYNDROMES IN GYNECOLOGY

Учебно-методическое пособие

Минск БГМУ 2025

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Освещены вопросы нейроэндокринных заболеваний в гинекологии, современные аспекты этиологии и патогенеза, клинической картины, диагностики и терапии данной патологии.

Предназначено для студентов 5-го курса медицинского факультета иностранных учащихся, обучающихся на английском языке по дисциплине «Акушерство и гинекология».

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ABBREVIATIONS

PMS — Premenstrual syndrome
GABA — γ-aminobutyric acid
SSRI — Selective Serotonin Reuptake Inhibitors
SNRI — Selective Noradrenaline Reuptake Inhibitors
COC — Combined oral contraceptive
IUS — Intrauterine system
GnRH — Gonadotropin releasing hormone
STRAW — Stages of Reproductive Aging Workshop
FSH — Follicular stimulating hormone
LH — Luteinizing hormone
FMP — Final menstrual period
HDL — High-density lipoprotein
LDL — Low density lipoprotein
BMI — body mass index
DEXA — Dual-energy X-ray absorptiometry
HRT — Hormone replacement therapy
DHT — Dihydrotestosterone
DHEA — Dehydroepiandrosterone
SHBG — Sex hormone-binding globulin
PCOS — Polycystic ovarian syndrome
IGF-1 — insulin growth factor-1
CAH — Congenital adrenal hyperplasia

MOTIVATIONAL CHARACTERISTIC OF THE TOPIC

Lesson topic: Neuroendocrine syndromes in gynecology.
Total class time: 6 academic hours.

The problem of neuroendocrine disorders in gynecology is relevant and essential in the training of a doctor due to an increase of the frequency of menstrual cycle disorders, infertility and miscarriage, gestational pathology and comorbid pathology, which are often associated with polycystic ovarian syndrome and congenital adrenal hyperplasia in women. Premenstrual disorders and premenstrual dysphoric pathology and menopausal syndrome significantly deteriorate a woman's health. At the same time, this problem is at the junction of specialties, is relevant for all age groups and has a socially significant character due to the variety of symptoms, the chronic course of the disease and a significant decrease in the quality of life of patients what require deep knowledge of the etiology, pathogenesis, diagnosis and treatment of the neuroendrocrine syndromes.

The purpose of the lesson: to study the most common neuroendocrine syndromes in gynecological practice: polycystic ovary syndrome, congenital adrenal hyperplasia, hirsutism and virilization, premenstrual and menopausal syndromes.

Lesson objectives:

1. To learn taking medical and family history, general and special gynecological care in women with neuroendocrine pathology.
2. To study modern theories of etiology and pathogenesis, methods of diagnosis and treatment neuroendocrine syndromes.
3. To learn how to evaluate anamnestic data, the results of objective and laboratory examination methods and imaging techniques in women with neuroendocrine pathology.
4. To master the practical skills of gynecological examination of women, additional examination methods.

The student should know:

1. The frequency and role of neuroendocrine syndromes in the general structure of gynecological pathology.
2. Clinical and laboratory tests in patients depending on the type of neuroendocrine syndrome.
3. Etiology, pathogenesis, classification, clinical signs, diagnosis, differential diagnosis, treatment and prevention of neuroendocrine syndromes.
4. Fundamentals of treatment and rehabilitation and medical examination of patients with neuroendocrine syndromes.

The student must be able:

1. To take a general medical and family history and obstetric-gynecological anamnesis in patients with neuroendocrine syndromes.
2. To conduct a general and special gynecological examination and assess the general condition of the patient.
3. To interpret the results of clinical examination and laboratory tests of patients with neuroendocrine syndromes for the diagnosis and differential diagnosis of the pathology.
4. To identify risk factors for the development of neuroendocrine syndromes.

Requirements for the initial level of knowledge. In order to assimilate the topic completely, it is necessary to repeat the following educational data from:

– anatomy: the structure of the genitals and adrenal glands in different age periods;

– histology, cytology, embryology: the development (ontogenesis) of the genital organs, adrenal glands in different age periods;

– normal physiology: physiological changes and functions of the reproductive organs and adrenal glands in different age periods;

– biochemistry: hormones and their structure, effects in relation to the reproduction;

– pharmacology: hormonal drugs and their effect on a woman's body;

– endocrinology: the endocrine system in girls and women at different age periods.

NEUROENDOCRINE SYNDROMES

Neuroendocrine syndromes are conditions which associated with pathological changes in the central nervous and endocrine systems simultaneously. Neuroendocrine gynecological syndromes have a common pathogenesis with a basis of deterioration of the hypothalamic-pituitary axis, as the most important feedback in the regulation of generative function of the female body, however, each of these syndromes is characterized by a predominance of symptoms that determine the specific manifestations.

PREMENTRUAL SYNDROME AND PREMENSTRUAL DYSPHORIC DISORDERS

Premenstrual disorders affect up to 12 % of women. The subspecialties of psychiatry and gynecology have developed overlapping but distinct diagnoses that qualify as a premenstrual disorder; these include premenstrual syndrome and premenstrual dysphoric disorder. These conditions encompass psychological and physical symptoms that cause significant impairment during the luteal phase of the menstrual cycle, but resolve shortly after menstruation.

Premenstrual disorders consist of psychiatric or somatic symptoms that develop within the luteal phase of the menstrual cycle, affect the patient's normal daily functioning, and resolve shortly after menstruation. The luteal phase begins after ovulation and ends with the start of menstruation. The subspecialties of psychiatry and gynecology have developed overlapping but distinct diagnoses that qualify as a premenstrual disorder. The American Collegue of Obstetricians and Gynecologists includes psychiatric and physical symptoms in describing premenstrual syndrome. The American Psychiatric Association focuses predominantly on psychiatric symptoms in its diagnostic criteria for premenstrual dysphoric disorder.

Definition. Premenstrual syndrome (PMS) is a psychoneuro-endocrine disorder of unknown etiology, often noticed just prior to menstruation. There is cyclic appearance of a large number of symptoms during the last 7–10 days of the menstrual cycle.

Following criteria should be in PMS:

– not related to any organic lesion;

– regularly occurs during the luteal phase of each ovulatory menstrual cycle;

– symptoms must be severe enough to disturb the life style of the woman or she requires medical help;

– symptom-free period during rest of the cycle.

When these symptoms disrupt daily functioning with severe presentation of 5–11 core signs they are grouped under the name premenstrual dysphoric disorder (PMDD).

Pathophysiology. Premenstrual syndrome is not due to a single factor. Genetic, environmental, and psychological are important factors in mood disorders as well as hormonal influence.

There are the following hypotheses:

1. The most common theory is alteration in the level of estrogen and progesterone starting from the midluteal phase. Either there is altered estrogen: progesterone ratio or diminished progesterone level. The consensus is that serum ovarian steroid concentrations are normal in these women and interactions of fluctuating levels of ovarian steroids or their metabolites with neurotransmitter systems or receptor imbalances in the brain are directly relevant to the pathogenesis of PMS (fig. 1).

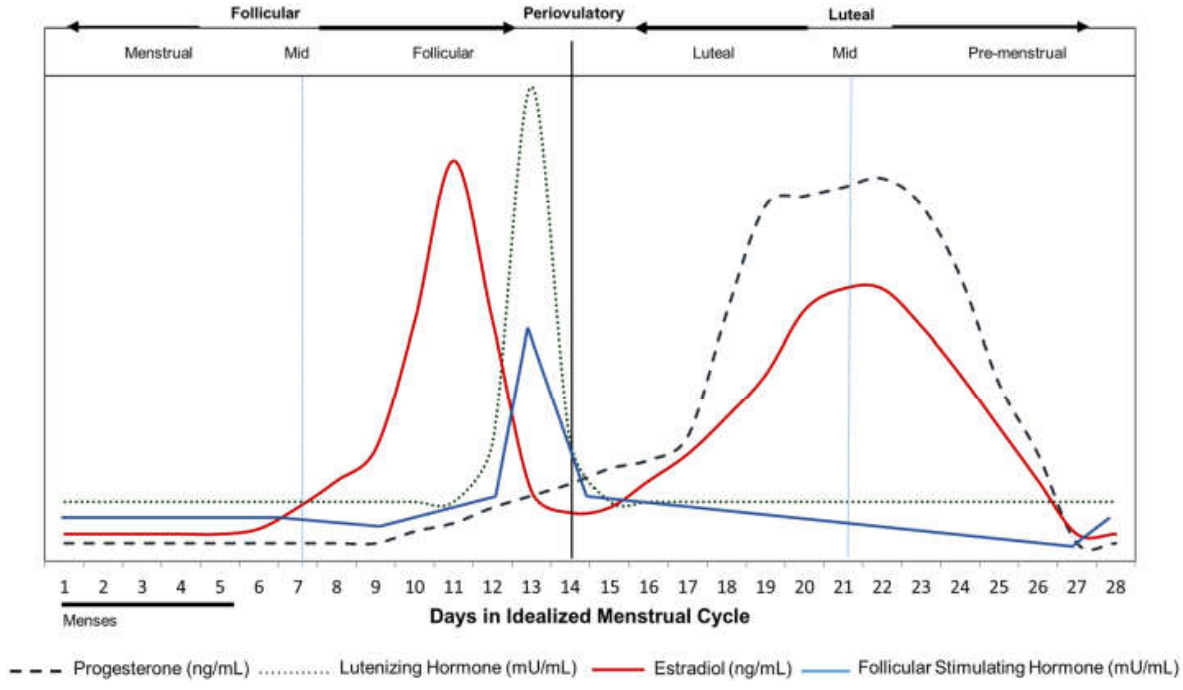

Fig. 1. Fluctuations in hormone levels during the menstrual cycle

This is believed to render women more sensitive to physiological levels of progesterone. Throughout reproductive life progesterone has an influence on women's physical/psychological health. Progesterone and its metabolites such as allopregnanolone are produced by the ovary and the adrenals, and also de novo in the brain. These hormones themselves are neurosteroids that readily cross the blood–brain barrier. Progesterone has a sedative effect when administered. Estrogen has effects on several neurotransmitters, including serotonin, acetylcholine, noradrenaline and dopamine. It cumulatively acts as an agonist on serotonergic function by increasing the number of serotonin receptors, serotonin (5-HT) postsynaptic responsiveness and neurotransmitter transport and uptake. It also increases serotonin synthesis and boosts the levels of the metabolite 5-hydroxyindoleaceticacid (5-HIAA). It is well known that the serotonergic system plays a substantial role in regulating mood, sleep, sexual activity, appetite and cognitive ability. Serotonin is a major component in the development of depression. This hypothesis is supported indirectly by the observation that serotonin-receptor concentrations vary with changes in estrogen and progesterone level.

2. Neuroendocrine factors:

– serotonin is an important neurotransmitter in the central nervous system. During the luteal phase, decreased synthesis of serotonin is observed in women suffering from PMS;

– endorphins: the symptom complex of PMS is thought to be due to the withdrawal of endorphins (neurotransmitters) from central nervous system during the luteal phase;

– γ-aminobutyric acid (GABA) suppresses the anxiety level in the brain. Estrogen increases binding of GABA agonists and the upregulation of GABA receptors. Medications that are GABA agonist, are effective.

3. Psychological and psychosocial factors may be involved to produce behavioral changes.

4. Vitamin B6 (pyridoxine) is a cofactor in the final step in the synthesis of serotonin and dopamine from dietary tryptophan. However, no data have yet demonstrated consistent abnormalities either of brain amine synthesis or deficiency of cofactors such as vitamin B6.

5. Others. Variety of factors have been mentioned to explain the symptom complex of PMS. These are thyrotrophin releasing hormone, prolactin, renin, aldosterone, prostaglandins, and others. But nothing is conclusive.

Clinical features. Symptoms of PMS (a wide range of symptoms has been described but it is their timing and severity that are most important, more so than the specific character):

1. Related to water retention:

– abdominal bloating;

– breast tenderness;

– swelling of the extremities;
– weight gain.

2. Neuropsychiatric symptoms:

– irritability;
– depression;
– mood swings;
– forgetfulness;
– restlessness;
– increased appetite;
– tearfulness;
– anxiety;
– tension;
– confusion;
– headache;
– anger.

3. Behavioral symptoms:

– fatigue;
– dyspareunia;
– tiredness;
– insomnia.

Because most normal women have some degree of symptomatology in the days leading up to the period it is considered that it is the severity of symptoms, namely that they significantly disrupt normal functioning, that distinguishes those women with PMS from those with no more than physiological premenstrual symptoms.

Diagnosis. There are no objective tests (physical, biochemical or endocrine) to assist in making the diagnosis. Prospectively completed specific symptom charts are required.

This is partly because the retrospective reporting of symptoms is inaccurate and because significant numbers of women who present with PMS have another underlying problem such as the perimenopause, thyroid disorder, migraine, chronic fatigue syndrome, irritable bowel syndrome, seizures, anaemia, endometriosis, drug or alcohol abuse, menstrual disorders as well as psychiatric disorders such as depression, bipolar illness, panic disorder, personality disorder and anxiety disorder.

The confirmation of luteal phase timing with the relief of symptoms by the end of menstruation is diagnostic providing the symptoms are of such severity to impaction the patient's normal functioning. It is also important to exclude patients who have a premenstrual exacerbation of an underlying psychological disorder among several others.

To meet the diagnostic criteria for PMDD, a patient must have at least five of the symptoms in the week before menses, and these symptoms must improve within a few days after the onset of menses.

Diagnostic Criteria for Premenstrual Dysphoric Disorder:

A. In the majority of menstrual cycles, at least five symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week postmenses.

B. One (or more) of the following symptoms must be present:

1. Marked affective lability (e. g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection).

2. Marked irritability or anger or increased interpersonal conflicts.

3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts.

4. Marked anxiety, tension, and/or feelings of being keyed up or on edge.

C. One (or more) of the following symptoms must additionally be present, to reach a total of five symptoms when combined with symptoms from Criterion B above.

1. Decreased interest in usual activities (e. g., work, school, friends, hobbies).

2. Subjective difficulty in concentration.

3. Lethargy, easy fatigability, or marked lack of energy.

4. Marked change in appetite; overeating; or specific food cravings.

5. Hypersomnia or insomnia.

6. A sense of being overwhelmed or out of control.

7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of «bloating», or weight gain.

NOTE: The symptoms in Criteria A-C must have been met for most menstrual cycles that occurred in the preceding year.

D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e. g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).

E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).

Confirmation of the disorder:

F. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (NOTE: The diagnosis may be made provisionally before this confirmation).

G. The symptoms are not attributable to the physiologic effects of a substance (e. g., a drug of abuse, a medication, other treatment) or another medical condition (e. g., hyperthyroidism).

Treatment. Due to the multifactorial etiology of PMS various drugs are used either on speculation or empirically with varying degrees of success.

Nonpharmacological therapy. Diet recommendations emphasize eating fresh rather than processed foods. The patient is encouraged to eat more fruits and vegetables and minimize refined sugars and fats.

Minimizing salt intake may help with bloating, and eliminating caffeine and alcohol from the diet can reduce nervousness and anxiety. None of these therapies have shown statistically significant improvements in PMS and PMDD, but they are reasonable, benign, a good part of general health improvement, and in some studies have demonstrated trends towards improvement. Clearly these interventions yield low risks and are generally healthful behaviors.

Lifestyle interventions that have demonstrated significant improvement in symptoms include aerobic exercise and calcium carbonate and magnesium supplementation. Aerobic exercise, as opposed to static (e. g., weight lifting) exercise, has been found to be helpful in some patients, possibly by increasing endogenous production of endorphins.

Calcium decreases water retention, food cravings, pain, and negative affect, compared with placebo.

Pharmacological therapy.

Nonhormonal therapy:

a) tranquilizers or antidepressant drugs;

b) pyridoxine (vitamin B6) — 100 mg twice daily is helpful by correcting tryptophan metabolism specially following ‘pill’ associated depression;

c) diuretics in the second half of the cycle — Furosemide 20 mg daily for consecutive 5 days a week reduces fluid retention;

d) anxiolytic agents are found to be helpful to women having persistent anxiety. Alprazolam 0.25 mg) is given during the luteal phase of the cycle;

e) selective Serotonin Reuptake Inhibitors (SSRI) and Noradrenaline Reuptake Inhibitors (SNRI) are found to be very effective. SSRIs effect via increasing serotonin levels by inhibiting neuronal uptake of serotonin. Fluoxetine 20 mg daily is usually sufficient to improve psychiatric and behavioral symptoms in most women. Side effects such as loss of libido may be partially avoided by administering the drug only during the luteal phase. Surprisingly the effect of the SSRIs is more instantaneous for PMS symptoms than is the case for depression. The drugs are usually prescribed at least two days prior to the onset of symptoms and to be continued till menstruation starts.

Other drugs used are: Sertaline (50 mg/day) and Venlafaxine.

Hormonal therapy:

1. Combined Oral contraceptive pills (COC). The concept is to suppress ovulation and to maintain an uniform hormonal milieu (fig. 2). Duration of the therapy is 3–6 cycles. Preferable COCs is one which contain progestin drospirenone. It has antimineralocorticoid and antiandrogenic effects. That's why Drospirenone containing COCs are considered to have better control of symptoms.

2. Progesterone is not effective in treatment of PMS. Levonorgestrel intrauterine system (IUS) had been used to suppress ovarian cycle. The intrauterine progestogen provides endometrial protection without achieving systemic levels that would act on the central nervous system reintroducing the PMS symptoms. This combination would have the added benefit of improving any menstrual problems and would provide contraception. There is only limited evidence that exists for this combination — suppression of ovarian function with oestrogen has clearly been shown to eliminate the symptoms. The Mirena IUS reduces the incidence of endometrial hyperplasia.

3. Spironolactone (a potassium sparing diuretic) has anti-mineralocorticoid and anti-androgenic effects. It is given in the luteal phase (25–200 mg/day) for improvement of the symptoms of PMDD and bloating.

4. Bromocriptine: 2.5 mg daily or twice daily may be helpful, at least to relieve the breast complaints.

Suppression of ovarian cycle. Suppression of the endogenous ovarian cycle can be achieved by:

1. Danazol 200 mg daily is to be adjusted so as to produce amenorrhea. Barrier method of contraception should be advised during the treatment.

2. GnRH analogues. The gonadal steroids are suppressed by administration of GnRH agonist for 6 months (which is equal medical oophorectomy). Goals of administration of GnRH analogues in PMS are:

– to assess the role of ovarian steroids in the etiology of PMS;

– this can also predict whether bilateral oophorectomy would be of any help or not;

– Goserelin (Zoladex): 3.6 mg is given subcutaneously at every 4 weeks;

– Leuprorelin acetate (Prostap): 3.75 mg is given by SC or IM at every 4 weeks;

– Triptorelin (Decapeptyl): 3 mg is given intramuscularly every 4 weeks.

As GnRH agonist therapy leads to amenorrhea and side effects similar to menopausal syndrome it should be combined with estrogen progestin «add-back» therapy to combat the hypoestrogenic symptoms.

3. Oophorectomy.

In certain cases of PMS with recurrence of symptoms and approaching to menopause as well as ineffective pharmacological treatment, hysterectomy with bilateral oophorectomy is a last choice.

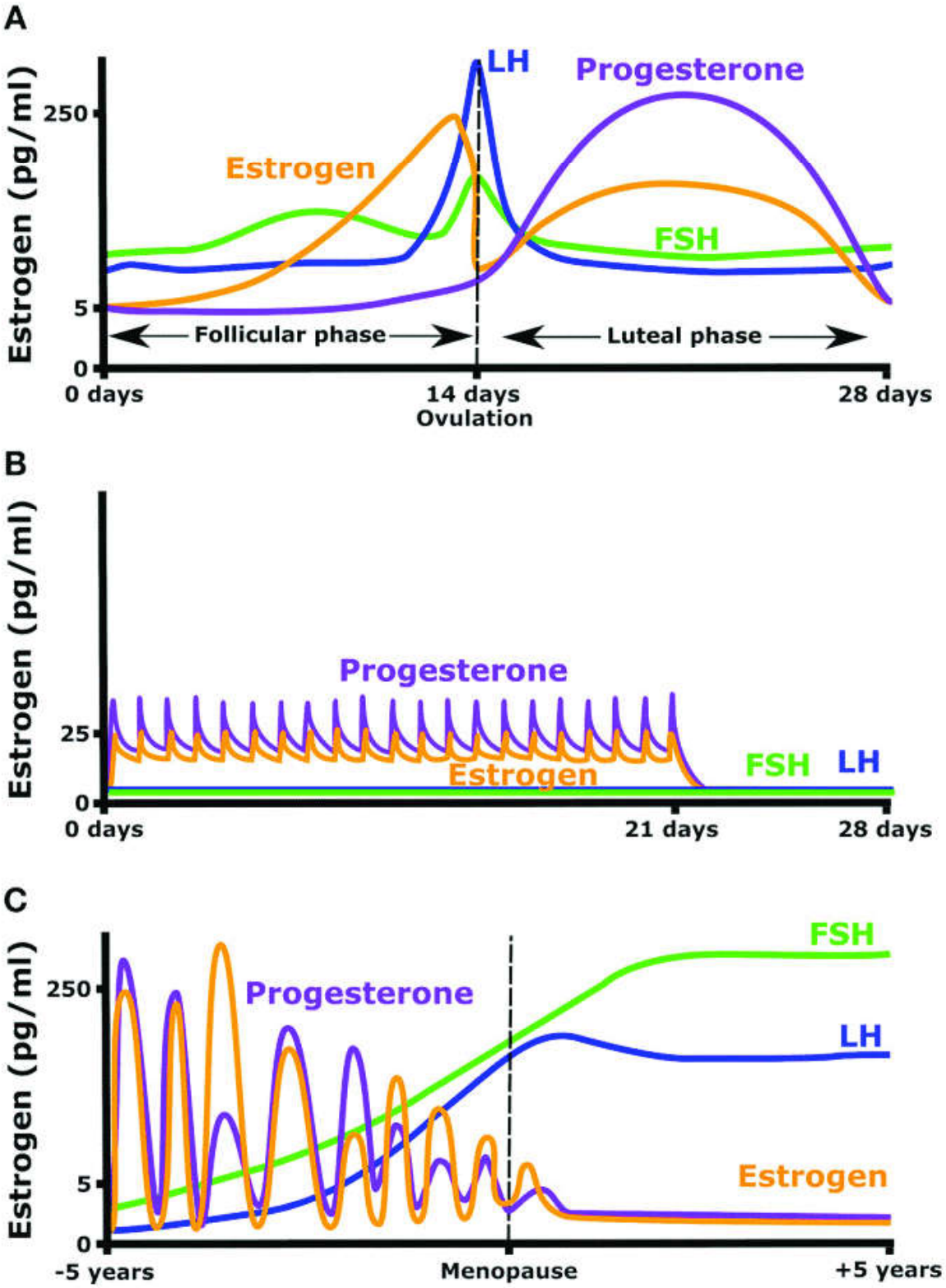

Fig. 2. Hormonal fluctuation during:
A — a normal menstrual cycle; *B* — while taking an oral contraceptive containing both estrogen and progesterone; *C* — in the years before and after menopause

MENOPAUSAL SYNDROME

Menopause means permanent cessation of menstruation due to loss of ovarian follicular pool. The clinical diagnosis is confirmed following stoppage of menstruation (amenorrhea) for twelve consecutive months without any other pathology.

Premenopause refers to the period prior to menopause, **postmenopause** to the period after menopause and perimenopause to the period around menopause (40–55 years).

Climacteric is the period of time during which a woman passes from the reproductive to the non- reproductive stage. This phase covers 5–10 years on either side of menopause.

Perimenopause is the part of the climacteric when the menstrual cycle is likely to be irregular.

In 2001, the Stages of Reproductive Aging Workshop (STRAW) standardized the nomenclature for the stages of the menopausal transition. Prior to this workshop, there was no accepted system for defining the stages of reproductive aging leading up to menopause. In 2010, at a follow-up workshop («STRAW + 10»), the criterion was updated to reflect advances in changes in the hypothalamic-pituitary function occurring throughout reproductive aging.

The STRAW staging system divides female life span into three broad phases: reproductive phase, menopausal transition phase, and postmenopause phase. Each of the three phases is divided into stages based on information obtained through clinical (menstrual cycle pattern, symptoms) and investigative (serum levels of follicle-stimulating hormone (FSH) and antimüllerian hormone (AMH) and ultrasound-based ovarian antral follicle count) data.

The menopausal transition is a finite period of physiologic changes that eventually culminates in reproductive senescence. This phase of life can be associated with unique challenges that can have significant effects on population's well-being and on quality of life.

Menopause is considered as amenorrheic period for a consecutive of 12-month interval and demonstrates biochemical evidence of hypergonadotropic (elevated FSH and luteinizing hormone [LH] levels) hypogonadism (low estradiol levels). The last or final menstrual period (FMP) is identified as stage «0» marking a watershed between reproductive and postreproductive periods of life.

The reproductive phase itself is broken down into five stages (early [−5], peak [−4], and late [−3]). The menopause transition phase is broken down into two stages (early [−2] and late [−1]). The postmenopause phase is also divided into two stages (early [+1] and late [+2]). The FMP thus serves as the reference point for interpretation of the rest of the stages across the three specified phases of reproductive aging.

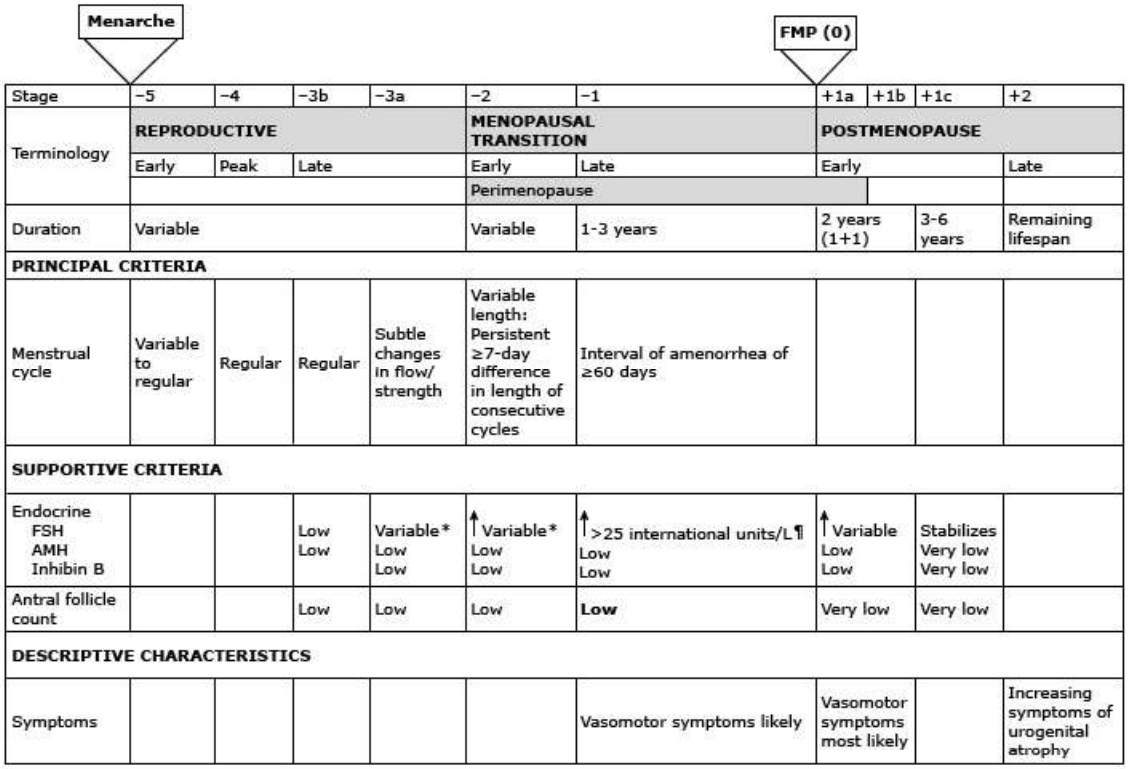

Fig. 3. The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women

Late Reproductive Stage (STRAW Stage −3). A decline in fecundability is apparent as the earliest hallmark of transition followed by a spectrum of changes in menstrual cycle pattern. As covert endocrinologic changes set in well before noticeable and clinically apparent features (such as changes in the menstrual cycle), STRAW +10 recommended that the late reproductive stage be divided into substages −3b and −3a. In stage −3b, the menstrual cycles are relatively unchanged, the early follicular phase serum levels of FSH are relatively low and in normal premenopausal range, whereas AMH and follicle count (and likely inhibin B) are low. In stage −3a, menstrual cycles become shorter and early follicular FSH increases, while AMH, follicle count, and inhibin B are low.

Early Menopausal Transition (STRAW Stage −2). This stage is characterized by increasing irregularity of the menstrual cycle length. This irregularity is defined as a recurrence of 7-day difference in cycle length over 10 cycles. This stage is also characterized by variable elevations in early follicular phase FSH levels, with persistently low AMH levels and low follicle count.

Late Menopausal Transition (STRAW Stage −1). This stage is characterized by missed menses with periods of amenorrhea lasting greater than or equal to 60 days. Menstrual cycles are increasingly irregular in length, with variability in reproductive hormonal levels and high incidence of anovulation. FSH levels are usually elevated in the menopausal range, although at times can

be in the premenopausal range with concomitant high estradiol levels. An FSH level of greater than 25 IU/L is commonly seen in this late transition stage. This stage lasts 1–3 years and is when vasomotor symptoms such as hot flushes begin to occur.

Early Postmenopause (STRAW Stage 1, Substages +1a, +1b, +1c). In the early postmenopause, FSH levels continue to rise, while estradiol levels continue to decline until 2 years after the FMP, after which these hormone levels stabilize. The substages +1a and +2b in early menopause last 1 year each and culminate once fluctuations in FSH levels stabilize. Stage +1a marks the completion of the 12-month interval required to define the FMP. This substage also marks the end of the perimenopause. Stage +1b includes the continued changes in levels of FSH and estradiol; vasomotor symptoms are most common in stage +1a and +1b. In stage +1c, the elevated FSH and low estradiol levels become the new normal. This substage lasts for up to 3–6 years. As such, the early postmenopause stage spans a total of 5–8 years.

Late Postmenopause (Stage +2). At this stage, reproductive hormone levels are essentially plateaued and stable. While the burden of vasomotor symptoms eases off for many, physical symptoms attributable to lack of estrogen, such as vaginal dryness and urogenital symptoms, become more prominent at this stage. Interestingly, FSH levels may decline further with age, although more research is needed to confirm this observation.

Age of Menopause. It is considered that age of menopause is genetically predetermined. The age of menopause is not related to age of menarche or age at last pregnancy, number of pregnancy, lactation, use of oral pill, socioeconomic condition, race, height or weight. Typically thinner women have early menopause. However, cigarette smoking and severe malnutrition may be associated to early menopause.

The average age of menopause is 50–51 years, ranging between 45–55 years.

An increasing proportion of women is included in this group. Two hundred years ago only 30 % of women lived through a menopause; and now, more than 90 % will. Thus, the menopause transition and postmenopause is a very important condition of the 20th and 21st centuries. Life expectancy is increasing all over the world. The majority of women can therefore expect to live over a third of their lives in a menopausal state.

Unfortunately, many of postmenopausal women have a progressively declining quality of life. That's why it's highly recommended optimization of menopause health care to reduce effects of menopause.

Pathophysiology of menapause. Hypothalamo-Pituitary-Gonadal Axis undergoes significant changes during perimenapause. Few years prior to menopause, along with declining of the ovarian follicular pool, the follicles become resistant to pituitary gonadotropins — FSH and LH. As a result, effective folliculogenesis

is impaired with diminished estradiol production. The level of serum estradiol is significantly falling from 50–300 pg/mL before menopause to 10–20 pg/mL after menopause. Deficiency of estrogen declines the negative feedback effect on hypothalamopituitary axis resulting in increase in FSH. The increase in FSH is also due to diminished inhibin B. Inhibin, a peptide, is secreted by the granulosa cells of the ovarian follicle. The increase of LH occurs in 2–3 years later, but just 2–3 times over due to short life of LH.

Abnormal folliculogenesis during this period results in anovulation, oligoovulation, premature corpus luteum or corpus luteal insufficiency. The sustained level of estrogens may cause endometrial hyperplasia and clinical manifestation of menstrual abnormalities prior to menopause.

The mean cycle duration is significantly shorter due to shortening of the follicular phase of the cycle. Luteal phase length remains constant.

Ultimately, no more follicles are available and even some exist. There is significant change in estrogens ratio. In the postmenopausal period, the predominant endogenous estrogen is estrone and to a lesser extent estradiol. The source of estrone is peripheral conversion (aromatization) of androgens from adrenals (mainly) and ovaries. The aromatization occurs in the adipose tissue. The trace amount of estradiol is derived from peripheral conversion of estrone and androgens. Compared to estradiol, estrone is biologically less potent. As synthesis of estrone is extragonadal its concentration is directly related to body weight.

After menopause, the theca cells of the ovary continue to produce androgens (androstenedione and testosterone) due to increased LH level. Though the secretion of androgens is increased, their peripheral levels are reduced because of conversion of androgens to estrone in adipose tissue. However, the estrogen: androgen ratio is decreased what leads to increased facial hair growth and change in voice.

As the obese patient converts more androgens into estrone, they are less likely to develop symptoms of estrogen deficiency and osteoporosis. But, they are vulnerable to endometrial hyperplasia and endometrial carcinoma.

Endocrine changes lead to dramatic anatomical and functional changes in the female body:

1. Ovaries shrink in size, cortex becomes thin and medulla in medulla and stroma — thick with abundance of stromal cells which has got secretory activity.

2. Fallopian tubes become atrophic.

3. The uterus becomes smaller and the ratio between the body and the cervix reverts to the 1 : 1. The endometrium is atrophic with absence of proliferation. In some women, however, with high endogenous estrogens, the endometrium may be proliferative or even hyperplastic. The cervical secretion becomes scanty.

4. The vagina becomes narrower and vaginal epithelium is thinning. The rugae are flat and not prominent. As a result of estrogen deficiency in the

epithelium intermediate cells dominate. Doderlein's bacillus is absent. The vaginal pH becomes alkaline.

5. The vulva transforms significantly becomes atrophic with a narrow introitus. The labia are flattened and the pubic hair are scantier.

6. Breast fat is reabsorbed and the glands atrophy. The nipples decrease in size.

7. Bladder and urethra undergo atrophic changes. The epithelium becomes thin and is more prone to damage and infection. There may be dysuria, frequency, urge or even stress incontinence.

8. Diminished muscle tone leads to pelvic floor relaxation, uterine descent and anatomic changes in the urethra and neck of the bladder.

Metabolic changes include bone metabolism. The balance between bone formation (osteoblastic activity) and bone resorption (osteoclastic activity) depends on many factors (age, endocrine, nutrition and genetic). After menopause, due to deficiency of estrogen there is loss of bone mass by about 3–5 % per year leading to osteoporosis. Osteoporosis is characterised by reduction in bone mass but bone mineral to matrix ratio is normal.

Whereas osteopenia refers to bone mineral density that is > 1.0 to < 2.5 standard deviation below the young adult mean bone mass («T»-score). Osteoporosis is > 2.5 SD below the young adult mean. There is a high risk for fracture of bones in menopause due to osteoporosis woman. Parathyroid hormone and IL-I are involved in osteoporosis.

Estrogen prevents osteoporosis by several mechanisms. It inhibits osteoclastic activity and inhibits release of IL-I by monocytes. Estrogen increases absorption of calcium from the gut, stimulates calcitonin secretion from the C cells of the thyroid and increases vitamin D.

Rate of cardiovascular disease is high in postmenopausal women. Estrogen prevents cardiovascular disease by several mechanisms:

– increases high-density lipoprotein (HDL) and decreases low density lipoprotein (LDL) and total cholesterol;

– inhibits platelet and macrophage (foam cell) aggregation at the vascular intima;

– stimulates the release of nitric oxide and prostacycline from vascular endothelium to dilate the blood vessels;

– prevents atherosclerosis by its antioxidant property.

Menstrual cycle abnormalities in perimenopause are very common:

– abrupt cessation of menstruation;

– gradual decrease in both amount and duration;

– irregular with or without excessive bleeding.

Menopausal clinical signs. Menopause is a physiologic process that can be associated with symptoms that may affect women's quality of life.

The clinical course of menopausal syndrome has its own patterns. Thus, by the time of occurrence, there are immediate, intermediate and long term symptoms.

Immediate symptoms include vasomotor symptoms and psychological changes.

Vasomotor symptoms. «Hot flush» is the commonest symptom of decreased estrogen production and is considered one of the hallmark sign of perimenopause. Hot flushes have a rapid onset and resolution. When a hot flush occurs, a woman feels a sudden sensation of warmth. The skin of the face and the anterior chest wall become flushed for approximately 90 seconds. With resolution of the hot flush, a woman feels cold and breaks out into a «cold sweat». The entire phenomenon lasts less than 3 minutes. As a woman approaches menopause, the frequency and intensity of hot flushes increase. Hot flushes may be disabling, especially at night. When perimenopausal and postmenopausal women receive hormone therapy, hot flushes usually resolve in 3 to 6 weeks. If a menopausal woman does not receive hormone therapy, hot flushes usually resolve spontaneously within 2 to 3 years, although some women experience them for 10 years or longer.

Hot flushes are considered to arise due to loss of estrogenic induced opioid activity in the hypothalamus leading to thermo-dysregulation. Hot flush coincides with GnRH pulse secretion with increase in serum LH level. It may last for 1–10 minutes. Sleep may be disturbed due to night sweats. The thermoregulatory center in association with GnRH center in the hypothalamus is involved in the etiology of hot flush.

Psychological changes include insomnia, anxiety, irritability, memory loss, tiredness and poor concentration. Mood disturbances can occur due to fluctuation in hormone levels leading to perimenopausal depression. Falling estrogen levels are thought to lead to similar falls in neurotransmitter levels such as serotonin which trigger these symptoms. Women who have suffered from post-natal depression and premenstrual syndrome appear to be particularly predisposed to depression in the perimenopause. The effect of menopause on cognitive function is unclear; some studies suggest a reduction in cognitive ability during the menopause transition, for example mathematical or visual-spatial tasks which can be improved with estrogen replacement. The probable mechanism is stimulating effect of estrogen in opioid (neurotransmitter) activity in the brain.

The menopause transition is also associated with a significant reduction in sexuality and libido. There are some pathophysiological reasons: decreased vaginal lubrication leading to dyspareunia, the reduction in androgen levels in post menapause. In fact, there are more androgen receptors in the female forebrain than in the male which modulate for psychosexual parameters. The decrease in androgens is particularly profound in women who have undergone early menopause or premature ovarian failure either spontaneously or due to iatrogenic intervention.

Intermediate symptoms:

1. Urogenital signs. Estrogen plays an important role to maintain the epithelium of vagina, urinary bladder and the urethra. Steroid receptors have been identified in the mucous membrane of urethra, bladder, vagina and the pelvic floor muscles. Estrogen deficiency leads to the rapid loss of collagen which contributes to the generalized atrophy after the menopause. In the genital tract this is manifested by dyspareunia and vaginal spotting from fragile and thin atrophic skin. Dyspareunia, vaginal infections, dryness, pruritus and leucorrhea are also common.

In the lower urinary tract, atrophy of the urethral epithelium occurs with decreased sensitivity of urethral smooth muscle and decreased amount of collagen in periurethral collagen. All this results in urgency, dysuria and recurrent urinary tract infection and stress incontinence, termed the urethro-genital syndrome.

More generalized changes are seen in the older woman as increased bruising and thin translucent skin which is vulnerable to trauma and infection. A similar loss of collagen from ligaments and joints may cause many of the generalized aches and pains so common in postmenopausal women.

2. Skin and hair changes. Due to deficiency of estrogen there are profound changes in skin and hair. Estrogen receptors are present in the skin and maximum are present in the facial skin. There is thinning, loss of elasticity and wrinkling of the skin. Skin collagen content and thickness decrease by 1–2 % per year. «Purse string» wrinkling around the month and «crow feet» around the eyes are the characteristics. After menopause, there is some loss of pubic and axillary hair and slight balding. This may be due to low level of estrogen with normal level of testosterone.

Long-term symptoms. Osteoporosis, cardiovascular disease and dementia are three long-term health problems which have been linked to the menopause.

Osteoporosis and fracture. Bone demineralization is a natural consequence of aging. Diminishing bone density occurs in both men and women. However, the onset of bone demineralization occurs 15 to 20 years earlier in women than in men by virtue of acceleration after ovarian function ceases. Bone demineralization not only occurs with natural menopause, but also has been reported in association with decreased estrogen production in certain groups of young women (such as those with eating disorders or elite athletes).

Estrogen receptors are present in osteoblasts, which suggests a permissive and perhaps even an essential role for estrogen in bone formation. Estrogen affects the development of cortical and trabecular bone, although the effect on the latter is more pronounced. Following menopause there is decline in collagenous bone matrix resulting in osteoporotic changes. Bone mass loss and microarchitectural deterioration of bone tissue occurs primarily in trabecular bone (vertebra, distal radius) and in cortical bones. Bone loss increases to 1–2 % per year during

menopause, compared 0,5 % in premenopausal women. Osteoporosis may be primary (Type 1) due to estrogen loss, age, deficient nutrition (calcium, vitamin D) or hereditary. It may be secondary (Type 2) to endocrine abnormalities (parathyroid, diabetes) or medication. Osteoporosis may lead to back pain, loss of height and kyphosis. Fracture of bones is a major health problem. Fracture may involve the vertebral body, femoral neck, or distal forearm (Colles' fracture). Morbidity and mortality in elderly women following fracture is high.

Risk factors for osteoporosis:

- age — elderly;
- family history;
- Race — asian, White race;
- lack of estrogen;
- body weight — low BMI;
- early menopause — surgical, radiation;
- Dietary — decreased calcium and decreased Vitamin D, increased caffeine;
- smoking;
- sedentary habit;
- Drugs — Heparin, corticosteroids, GnRH analogue;
- Diseases — Thyroid disorders, hyperparathyroidism;
- malabsorption, multiple myeloma.

Detection of osteoporosis: Computed tomography and specially the dual-energy X-ray absorptiometry (DEXA) are reliable methods to assess the bone-mineral density. Total radiation exposure is high with computed tomography than DEXA.

Biochemical parameters to detect bone loss are measurement of urinary calcium/creatinine and hydroxyproline/creatinine ratios.

Cardiovascular and cerebrovascular effects. Women are protected against cardiovascular disease before the menopause, after which the incidence rapidly increases reaching a similar frequency to men by the age of 70 years. The protective effect of estrogen in premenopausal women is thought to be mediated by an increase in HDL and a decrease in LDL, nitric oxide mediated vasodilatation leading to increased myocardial blood flow, an antioxidant effect on endothelial cells and a direct effect on the aorta decreasing atheroma.

In the deficit of estrogen there are oxidation of LDL and foam cell formation that cause vascular endothelial injury, cell death and smooth muscle proliferation. All these lead to vascular atherosclerotic changes, vasoconstriction and thrombus formation.

The protective role of estrogen in cardiovascular diseases is associated with a decrease in fibrosis, stimulation of angiogenesis and vasodilation, enhancement of mitochondrial function and reduction in oxidative stress.

Epidemiological evidence has shown that the most common risk factors for cardiovascular disease in menopausal women are central obesity, atherogenic dyslipidemia, glucose intolerance and hypertension. Increased sensitivity to sodium during menopause, which leads to fluid retention in the body causing swelling of the arms and legs, may also contribute to the cardiovascular risk.

The changes in hormone levels in the vascular system and metabolic changes that occur with age may be directly influenced by the increase in blood pressure, which is more common in postmenopausal women.

Risks of ischemic heart disease, coronary artery disease and strokes in post menopause are increased.

Adipose tissue in addition to being an energy storage is also an endocrine organ that produces adipokines such as leptin, resistin, adiponectin, and interleukin 6. Leptin is one of the biomarkers that may be used as an inflammation factor that may be considered to be responsible for interacting with the arterial wall. Leptin receptors are found in the aorta and blood vessels, and their level is related to the amount of adipose tissue. Studies have shown that that higher levels of leptin in plasma lead to obesity, hypertension, and other heart diseases.

A recent meta-analysis confirmed that women with early menopause (< 45 years) had a higher risk of arterial hypertension compared to women with menopause > 45 years.

The rise in systolic blood pressure is mainly caused by an increase in vascular stiffness of the great arteries in combination with atherosclerotic changes in the vessel wall. Systolic blood pressure rises more steeply in ageing women compared with men, and this may be related to the hormonal changes per se during menopause. The decline in the estrogen/androgen ratio dilutes the vasorelaxant effects of estrogens on the vessel wall and promotes the production of vasoconstrictive factors such as endothelin. Both male and female sex steroids have a regulating effect on the renin-angiotensin system (and affect angiotensinogen production and sodium metabolism. The decline in estrogen levels around menopause causes an upregulation of the renin-angiotensin system with an increase in plasma-renin activity. Oral estrogen replacement, however, increases the hepatic production of angiotensinogen, which is not observed with transdermal estrogen. Several clinical studies have shown that salt sensitivity is higher in postmenopausal women compared with premenopausal women, which may explain the effectiveness and good tolerance of diuretics and ACE inhibitors in ageing women. Further, sympathetic activity is higher in postmenopausal women than in age-matched men, especially in women who are overweight. Sympathethic overactivity is associated with abdominal visceral fat which is strongly related to increased inflammatory markers and oxidative stress. Another important change around menopause is an increase in insulin resistance which causes unfavourable changes in blood pressure, lipid metabolism, bodyweight and the development of the metabolic syndrome.

Dementia. Estrogen also appears to have a direct effect on the vasculature of the central nervous system and promotes neuronal growth and neurotransmission. Dementia and mainly Alzheimer disease are more common in postmenopausal women. Studies have demonstrated that estrogen may improve cerebral perfusion and cognition in women. In the long term this may prevent diseases with a vascular etiology such as vascular dementia and Alzheimer's as the vasculature is clearly involved in this. In addition to the effect on vasculature in Alzheimer's disease, estrogen may also intervene at the level of amyloid precursor protein.

Diagnosis of Menopause. The diagnosis of the menopause can usually be ascertained from a characteristic history of the vasomotor symptoms of hot flushes and night sweats and prolonged episodes of amenorrhoea. Measurement of plasma hormone levels in patients with classical symptoms are unnecessary, expensive, time consuming and of little clinical significance. However, in the young patient or in a woman after hysterectomy, where the diagnosis is more difficult and the metabolic implications are serious, measurement of FSH levels may be helpful.

There are following ***markers for diagnosis of menopause***:

1. Cessation of menstruation for consecutive 12 months during climacteric.
2. Appearance of menopausal symptoms «hot flush» and «night sweats».
3. Vaginal cytology — showing maturation index of at least 10/85/5.
4. Serum estradiol < 20 pg/mL.
5. Serum FSH and LH > 30 mIU/mL (three values at weeks interval required).

After the diagnosis has been established, investigations should be no more than the annual screening which is normally applicable to middle-aged women. This should include assessment of weight, blood pressure and routine cervical cytology. Fasting lipid profile estimation may be useful in women with risk factors not only from a general screening point but also if the patient is contemplating starting HRT.

Mammography should be performed as part of the national screening programme every 3 years unless more frequent examinations are clinically indicated. However, if a woman chooses to use HRT beyond the current age of breast screening cessation (65 years), mammographic screening should also continue. In women over 45 years of age it is best to arrange screening before starting estrogen therapy to identify patients with subclinical disease. Endometrial biopsy is not a necessary prerequisite to treatment with HRT unless there are symptoms of postmenopausal bleeding or irregular perimenopausal bleeding.

The best currently available measurement of osteoporosis risk is DEXA.

Management of menopause. Prevention. Spontaneous menopause is unavoidable. However, artificial menopause induced by surgery (bilateral oophorectomy) or by radiation (gonadal) during reproductive period can to some extent be preventable or delayed.

Every woman with postmenopausal symptoms should be adequately counselled about the physiologic events. This will remove her fears, and minimize or dispel the symptoms of anxiety, depression and insomnia. Reassurance is essential.

Treatment. Nonhormonal treatment:

1. Lifestyle modification includes:

– physical activity (weight bearing), reducing high coffee intake, smoking and excessive alcohol. There should be adequate calcium intake, reducing medications that causes bone loss (corticosteroids);

– nutritious diet — balanced with calcium and protein is helpful;

– supplementary calcium — daily intake of 1000–1500 mg can reduce osteoporosis and fracture;

– exercise — weight bearing exercises, walking, jogging;

– vitamin D — supplementation of vitamin D3 (1500–2000 IU/day) along with calcium can reduce osteoporosis and fractures;

– cessation of smoking and alcohol.

2. To prevent bone resorption, improve bone density and prevent fracture It should be preferred administration of bisphosphonates for older women. Monitoring of bone density measurement should be done.

The most common bisphosphonates are etidronate and alendronate. Alendronate is more potent. Ibandronate and zolendronic acid are also effective and have less side effects. Bisphosphonates when used alone cannot prevent hot flushes, atrophic changes and cardiovascular disease. It is taken in empty stomach. Nothing should be taken by mouth for at least 30 minutes after oral dosing. Side effects include gastric and esophageal ulceration, osteomyelitis and osteonecrosis of the jaw.

3. Selective estrogen receptor modulators are tissue specific in action. For example, raloxifene has shown to increase bone mineral density, reduce serum LDL and to raise HDL level. Raloxifene inhibits the estrogen receptors at the breast and endometrial tissues. Risks of breast cancer and endometrial cancer are therefore reduced. Raloxifene does not improve hot flushes or urogenital atrophy. Evaluation of bone density (hip) should be done periodically. Risks of venous thromboembolism is increased.

4. Alpha2 agonists. Clonidine, a centrally active alpha-2-agonist, has been one of the most popular alternative preparations for the treatment of vasomotor symptoms. Unfortunately it is also one of the preparations for which the least evidence exists for efficacy – at best the trial data show a weak benefit.

5. Beta-blockers. Beta blockers have been postulated as a possible option for treating vasomotor symptoms but the small trials which have been conducted.

6. Selective serotononin reuptake inhibitors (SSRIs) / Selective noradrenaline reuptake inhibitors (SNRIs). SSRIs and SNRIs are significantly effective in the

treatment of vasomotor symptoms. Although there are some data for SSRIs such as fluoxetine and paroxetine, the most convincing data are for the SNRI (venlafaxine) at a dose of 37.5 mg twice a day. The key effect with these preparations appears to be stimulation of the noradrenergic as opposed to the serotonergic pathways, hence the preferential effect of SNRIs. The trials demonstrate a 50–60 % reduction in hot flush frequency and severity. This compares with an 80–90 % symptom reduction with traditional hormone therapy. The main drawback with these preparations (especially the SNRIs) is the high incidence of nausea which often leads to withdrawal from therapy before maximum symptom relief efficacy has been achieved.

7. Gabapeptine is an analog of GABA. Gabapentin has shown efficacy for hot flush reduction compared to placebo. Gabapentin at a dose of 900 mg per day has been shown to reduce hot flush frequency by 45 % and symptom severity by 54 %.

Complementary treatment. ***Phytoestrogens*** are plant substances that have effects similar to those of estrogens. Since the first discovery of the estrogenic activity of plant compounds, over 300 plants have been found to have phytoestrogenic activity. Preparations vary from enriched foods such as bread or drinks (soy milk) to more concentrated tablets.

There two groups: isoflavones and lignans. The major isoflavones are genistein and daidzein. The major lignans are enterolactone and enterodiol.

Isoflavones are found in soybeans, chick peas, red clover and probably other legumes (beans and peas). Oilseeds such as flaxseed are rich in lignans, and they are also found in cereal bran, whole cereals, vegetables, legumes and fruit.

The role of phytoestrogens has stimulated considerable interest since populations consuming a diet high in isoflavones.

Alternative therapies for the short-term treatment of common symptoms of menopause include the following:

1. Soy and isoflavones may be helpful in the short-term (< 2 years) treatment of vasomotor symptoms. Given the possibility that these compounds may interact with estrogen, these agents should not be considered free of potential harm in women with estrogen-dependent cancers.

2. St. John's wort may be helpful in the short-term (< 2 years) treatment of mild to moderate depression in women.

3. Black cohosh may be helpful in the short-term (< 6 months) treatment of women with vasomotor symptoms.

4. Soy and isoflavone intake over prolonged periods may improve lipoprotein profiles and protect against osteoporosis. Soy in foodstuffs may differ in biological activity from soy and isoflavones in supplements.

Hormone replacement therapy or menopausal hormone therapy, or hormone replacement therapy (HRT), is a broad term describing estrogen monotherapy in women who have undergone hysterectomy and combined estrogen-progesterone/

progestogens therapy in women with an intact uterus, as well as other hormone therapy options. Estrogen therapy achieves the discharge of almost all menopausal symptoms such as vasomotor symptoms, which are associated with sleep, concentration disorders, reduced quality of life, urogenital atrophy up to the long-term prevention of chronic diseases whose direct association with lack of estrogen is not immediately visible.

To integrated menopause management the European Menopausal Society declared a 10-point guide for HRT:

– taking a right medical history, individual and family history, and clinical examination;

– diagnosis of menopausal status, e. g. premature ovarian failure;

– modification of the diet and lifestyle change;

– women should take part in population control programs for diseases in later life, e. g. screening for cervical, breast, bowel cancer;

– control of vasomotor symptoms with or without estrogen intake, emphasizing that HRT should be prescribed to symptomatic women under 60 years of age or within the first 10 years of menopause, as then the benefit outweighs the risk;

– the use of estrogen locally, at a low dose, is recommended when there are symptoms from the urogenital system only;

– protection of the musculoskeletal system and reduced risk of osteoporotic fractures and bone loss using HRT as well as SERMs, in women with premature ovarian insufficiency HRT should be administrated until they reach the normal age of menopause, unless there is a contraindication;

– contraception in perimenopause;

– continuous monitoring and reassessment.

Indication of Hormone Replacement Therapy:

– relief of menopausal symptoms;

– prevention of osteoporosis;

– to maintain the quality of life in menopausal years.

There are special group of women to whom HRT should be prescribed:

1. Premature ovarian failure.
2. Gonadal dysgenesis.
3. Surgical or radiation menopause.

Benefits of Hormone Replacement Therapy. Apart the side effects and risks that are likely to occur, HRT also offers significant benefits:

– improvement of vasomotor symptoms (70–80 %);

– improvement urogenital atrophy;

– increase in bone mineral density (2–5 %);

– decreased risk in vertebral and hip fractures (25–50 %) due to prevention of bone loss and stimulation of new bone formation;

– reduction in colorectal cancer (20 %);
– delay of atherosclerotic cardiovascular diseases and cardioprotection;
– improvement of lipid profile;
– reduction of insulin resistance, delaying and reducing the risk of developing type 2 diabetes.

Hormone therapy, although is a safe option for healthy symptomatic women, has absolute and relevant contraindications.

Risks of HRT:

1. Endometrial cancer: estrogen administered alone to a woman with intact uterus causes endometrial proliferation, hyperplasia and carcinoma.

2. Breast cancer: there is an excess risk of breast cancer using combined estrogen and progestogen HRT compared to estrogen alone.

3. Venous thromboembolic (VTE) disease is increased with the use of combined oral estrogen and progestin. Transdermal estrogen use does not have the same risk compared to oral estrogen.

4. Coronary heart disease: Combined HRT therapy shows a relative hazard of heart disease and hypertension.

5. Lipid metabolism: An increased incidence of gallbladder disease as estrogenic effect on rising in cholesterol (in bile).

Absolute contraindications of HRT are:

1. Undiagnosed vaginal bleeding.

2. Breast cancer: especially in women with an individual history, as women with a family history can receive treatment but have a higher basic risk than women without a family history. Combined estrogen and progestin replacement therapy, increases the risk of breast cancer slightly and risk is mostly associated with progestogen components.

3. Endometrial cancer: estrogen administered alone to a woman with intact uterus causes endometrial proliferation, hyperplasia and endometrial carcinoma.

4. Thromboembolic disease, stroke has been found to be increased with the use of combined oral estrogen and progestin. Transdermal estrogen use does not have the same risk compared to oral estrogen.

5. Coronary heart disease and congestive heart failure.

6. Active liver disease or dysfunction.

Oral estrogen should be avoided in women with hypertriglyceridaemia, active gallbladder disease, and known thrombophilia as lack of factor V Leiden or VIII Willebrandt.

Relevant contraindications include severe hypertension, increased cholesterol LDL, hypothyroidism, ovarian cancer, severe hypocalcemia, epilepsy, liver hemangioma, porphyria, endometriosis, asthma and migraine with aura.

Preparation for HRT. The principal hormone used in HRT is estrogen. In women with removed uterus (after hysterectomy) should be prescribed only

estrogen in monoregime. But in women with an intact uterus, only estrogen therapy leads to endometrial hyperplasia and recurrent withdrawal bleedings. To protect the endometrium progestins should be administered for last 12–14 days each month.

Commonly used estrogens are conjugated estrogen (0.625–1.25 mg/day) or micronized estradiol (1–2 mg/day).

The minimum dosages of currently available systemic oestrogen are as follows:

– 0.3–0.625 mg oral conjugated equine estrogens;
– 1 mg of oral micronized estradiol or estradiol valerate;
– 25–50 mcg transdermal estradiol;
– 25–50 mg of implanted estradiol;
– 150 mcg transnasal estradiol;
– 50 mcg estradiol silicone ring.

Data suggest that the benefits of a 2 mg dose of estradiol for symptoms and bone protection can be maintained by a 1 mg dose and similarly the benefits of a 50 mg estradiol implant are maintained by a 25 mg implant.

Local (vaginal) estrogen. Creams using estriol do not produce endometrial hyperplasia and the 17B estradiol vaginal tablet and silicone vaginal ring also provide effective relief of local symptoms (due to vaginal atrophy) without any significant endometrial effects. These preparations can be used without progestogenic opposition.

Options for local vaginal estrogen are as follows:

– 0.01 % estriol cream and pessaries;
– 0.1 % estriol cream;
– 25 mcg/24 h estradiol vaginal tablets;
– 7.5 mcg/24 h estradiol releasing silicone ring;
– premarin cream — this preparation can potentially cause endometrial hyperplasia and should not be used without progestogenic opposition for more than 3 months.

Progestins used are medroxyprogesterone acetate (2.5–5 mg/day), micronized progesterone (100–300 mg/day) or dydrogesterone (5–10 mg/day) or Levonorgestrel (IUS) 20 mcg (10 mcg in development).

Progestins side effects. It is vital to maximize compliance and receive the full benefits from HRT. One of the main factors for reduced compliance is that of progestogen intolerance. Progestogens have a variety of side effects:

1. Symptoms of fluid retention are produced by the sodium retaining effect of the renin-aldosterone system which is triggered by stimulation of the mineralocorticoid receptor.

2. Androgenic side effects such as acne and hirsuitism (usually for testosterone derived progestogens due to stimulation of the androgen recep-tors).

3. Mood swings and PMS-like side effects result from stimulation of the central nervous system progesterone receptors.

Testosterone preparations. Numerous studies have shown that adding testosterone to hormonal therapy can improve sexual function and general wellbeing among women during their menopause. It has also been shown to have additional benefits including the improvement of urogenital, psychological, and somatic symptoms, an increase in bone density, and enhancement of cognitive performance in combination with estrogen as part of HRT. Many women notice that taking testosterone improves their mood, concentration, motivation, and energy levels.

There is only 100 mg per 6 months implanted testosterone pellets are licensed for use in women; 25 mg pellets exist but must be ordered on a named patient basis.

Testosterone gel is used in 50 mg, 5 ml sachets at a dose of 0.5–1.0 ml day.

The normal range of testosterone is difficult to define as most of the available tests do not provide the accuracy or precision required when testing the low serum concentrations in women. As most testosterone is protein bound to sex hormone-binding globulin (SHBG), there is only a small circulating free fraction, which is difficult to measure reliably. The level of bioavailable testosterone can be estimated using free androgen index. It has been suggested that in a symptomatic woman with a free androgen index of < 1 %, a trial of testosterone supplementation could be considered. If the free androgen index is kept within the physiological range there are rarely any side effects such as hirsuitism. Levels should be checked at baseline and repeated at 4–6 weeks.

Research has suggested a neutral effect on the cardiovascular system, for example, arterial compliance and lipid effects.

Tibolone: Tiboloneisasteroid (19-nortestosterone derivative) having weakly estrogenic, progestogenic and androgenic properties. It prevents osteoporosis, atrophic changes of vagina and hot flushes. It increases libido. Endometrium is atrophic. A dose of 2.5 mg per day is given.

Monitoring Prior to and during HRT. It is mandatory to monitor a base level parameter of the following (at least annually):

– physical examination including pelvic examination;
– blood pressure recording;
– breast examination and mammography;
– cervical cytology;
– pelvic ultrasonography to measure endometrial thickness (normal < 4 mm);
– any irregular bleeding should be investigated thoroughly (endometrial biopsy, hysteroscopy).

Ideal serum level of estradiol should be 100 pg/ml during HRT therapy. serum level of estradiol is useful to monitor the HRT therapy rather than that of serum FSH.

PREMATURE OVARIAN FAILURE

Premature ovarian insufficiency (failure) is defined as ovarian failure before the age of 40 years. It occurs in approximately 1 % of the female population. During intrauterine life either there is failure of germ cell migration or there may be normal germ cell migration but an accelerated rate of germ cell depletion (apoptosis) due to various reasons. This results in either no follicle or only few follicles left behind in the ovary by the time they reach puberty.

Causes of premature ovarian failure:

1. Genetic: Turner's syndrome (45X0), (45X/46XX), gonadal dysgenesis 46XX, 46XY, trisomy 18 and 13, X-chromosome deletion, translocation.
2. Autoimmune: Autoantibodies: antinuclear antibodies, lupus anticoagulant, polyglandular autoimmune syndrome (antibodies against thyroid, parathyroid, adrenal, islet cells of pancreas).
3. Infections: mumps, tuberculosis.
4. Iatrogenic: radiation therapy, chemotherapy (cyclophosphamide), surgery. Chemotherapy and radiation therapy are most common causes of toxin0induced ovarian insufficiency due to damage of genetic material in cells.
5. Metabolic: galactosemia, 17α hydroxylase deficiency. Follicles are destroyed due to toxic effects of galactose.
6. Environmental: smoking.
7. FSH receptor absent or postreceptor defect (Savage's syndrome).
8. Idiopathic.

Complications:

1. Infertility.
2. Osteoporosis.
3. Depression and anxiety.
4. Cardiovascular pathology.
5. Dementia.
6. Parkinson's disease.

Diagnosis:

1. A medical history and history of amenorrhea in less than 35 years of age.
2. Pregnancy test.
3. Laboratory tests: serum FSH is high (> 40 IU/mL); serum estradiol < 20 pg/mL, antimullerian hormone (as a marker for ovarian insufficiency) is less than 1 (but it is not essential for diagnosis).
4. Karyotype abnormality.
5. Organ specific humoral antibody (antithyroid commonest).
6. Ovarian biopsy (afollicular, follicular and autoimmune variety) is not essential to the diagnosis. Ovarian ultrasound – there is no follicles.
7. Amenorrhea — primary (25 %) or secondary (75 %).

8. Symptoms of hypoestrogenic state like hot flushes, vaginal dryness, dyspareunia and psychological symptoms are there.

9. The possibility of autoimmune disorders should be considered below the age of 35. For this, antithyroid antibodies, rheumatoid factor and antinuclear antibodies should be measured.

10. In younger patients (age below 30) karyotype is to be done to rule out chromosomal abnormality.

Treatment is largely based on estrogen repletion to diminish vasomotor symptoms, maintain bone density, decrease fracture risk, decrease cardiovascular and autoimmune morbidity and mortality, protect cognitive function and improve well-being of the patients affected. The objective of the treatment is to insure that women diagnosed with premature ovarian failure maintain a daily level of 100 pg/ml of estradiol. The treatment should be continued until the average age of menopause (50 years old).

ANDROGEN EXCESS DISORDERS

Hirsutism is excess terminal hair in a male pattern of distribution. It is manifested initially by the appearance of midline terminal hair. Terminal hair is darker, coarser, and kinkier than vellus hair, which is soft, downy, and fine. It might be physiological or constitutional Care must be taken to evaluate the possibility that excess terminal hair is familial, not pathological, in origin.

The original system assessing of hirsutism (Ferriman-Gallwey) is based on the scoring of the presence of hair in 11 regions. When a woman is exposed to excess androgens, terminal hair first appears on the lower abdomen and around the nipples, next around the chin and upper lip, and finally between the breasts and on the lower back. Usually, a woman with hirsutism also has acne. For women in Western cultures, terminal hair on the abdomen, breasts, and face is considered unsightly and presents a cosmetic problem. As a result, at the first sign of hirsutism, women often consult their physician to seek a cause for the excess hair growth and seek treatment to eliminate it.

The Ferriman-Gallwey system was modified to include nine regions. A modified Ferriman-Gallwey scale used for the evaluation of hirsutism is shown in fig. 4. According to the modified Ferriman-Gallwey scoring system, each region is separately evaluated in terms of the rate of terminal hair growth and scored from 0 (absence) to 4 (excessive). The total score calculated of ≥ 8 is accepted as hirsutism. The severity of hirsutism was classified as mild if the score is 8–16, moderate if 17–24, and severe if above 24.

Hirsutism and virilization may be clinical clues to an underlying androgen excess disorder.

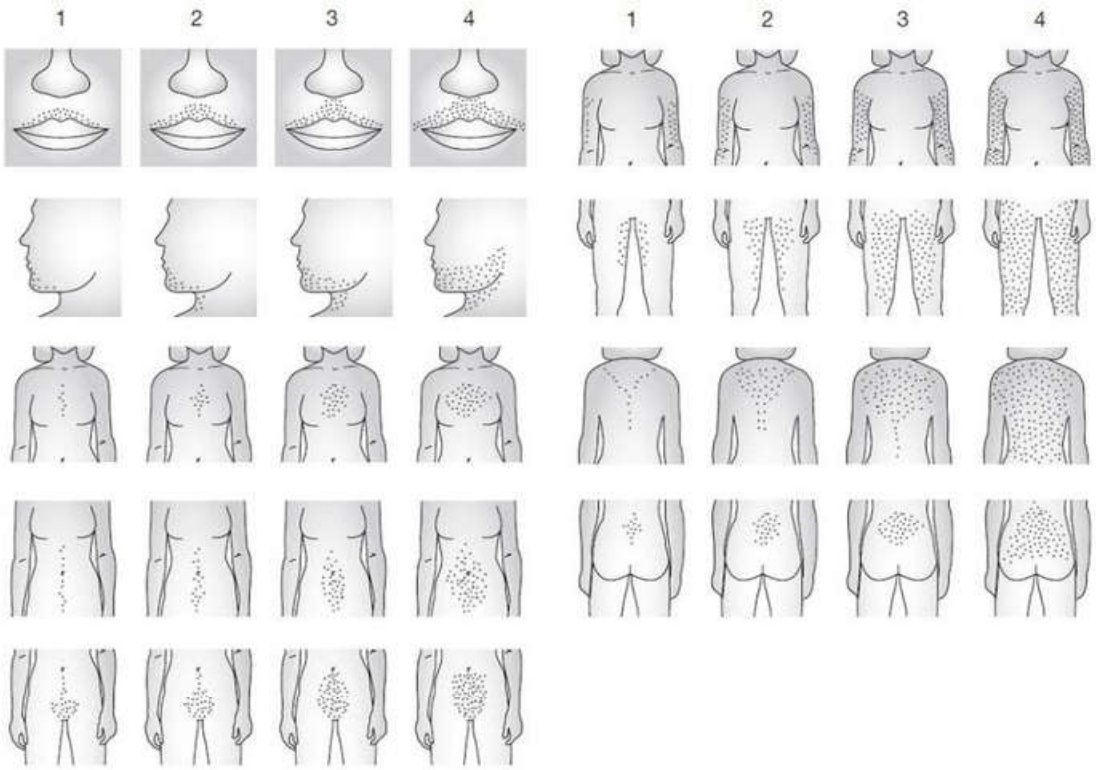

Fig. 4. A modified Ferriman-Gallwey scale for hirsutism assessing

Virilization is defined as masculinization of a woman and is associated with a marked increase in circulating testosterone. As a woman becomes virilized, she first notices enlargement of the clitoris, followed by temporal balding, deepening of the voice, involution of the breasts, and a remodeling of the limb-shoulder girdle as well as hirsutism. Over time, she takes on a more masculine appearance.

Idiopathic (constitutional or familial) hirsutism (a diagnosis of exclusion) is the most common nonpathologic etiology, representing about one-half of all cases. The most common pathologic causes of hirsutism are polycystic ovarian syndrome, followed by congenital adrenal hyperplasia. These conditions must be diagnosed by laboratory evaluations. Treatment of androgen excess should be directed at sup- pressing the source of androgen excess or blocking androgen action at the receptor site.

Androgen production and androgen action. In women, androgens are produced in the adrenal glands, the ovaries, and adipose tissue, where there is extraglandular production of testosterone from androstenedione. The following three androgens may be measured when evaluating a woman with hirsutism and virilization:

1. Dehydroepiandrosterone(DHEA): a weak androgen secreted principally by the adrenal gland (generally measured as dehydroepiandrosterone sulfate [DHEA-S] because of its longer half-life, making it a more reliable measure).

2. Androstenedione: a weak androgen secreted in equal amounts by the adrenal glands and ovaries.

3. Testosterone: a potent androgen secreted by the adrenal glands and ovaries and produced in adipose tis- sue from the conversion of androstenedione.

The sites of androgen production and proportions produced are presented in table 1. In addition, testosterone is also converted within hair follicles and within genital skin to dihydrotestosterone (DHT), which is an androgen even more potent than testosterone. This metabolic conversion is the result of the local action of 5α-reductase on testosterone at these sites. This is the basis for constitutional hirsutism.

Table 1

Sites of androgen production

Site	DHEA-s (%)	Androstendione (%)	Testosterone (%)
Adrenal glands	90	50	25
Ovaries	10	50	25
Extraglandular	0	0	50

Adrenal androgen production is controlled by reciprocal feedback regulation through pituitary secretion of adrenocorticotropic hormone. Adrenocorticotropic hormone stimulates the adrenal cortical production of cortisol. In the metabolic sequence of cortisol production, DHEA is one precursor hormone. In enzymatic deficiencies of adrenal steroidogenesis (21-hydroxylase deficiency and 11β-hydroxylase deficiency), DHEA accumulates and is further metabolized to androstenedione and testosterone.

Ovarian androgen production is regulated by LH secretion from the pituitary gland. LH stimulates theca-lutein cells surrounding the ovarian follicles to secrete androstenedione and, to a lesser extent, testosterone. These androgens are precursors for estrogen production by granulosa cells of the ovarian follicles. In conditions of sustained or increased LH secretion, androstenedione and testosterone increase.

Extraglandular testosterone production occurs in adipocytes (fat cells) and depends on the magnitude of adrenal and ovarian androstenedione production. When androstenedione production increases, there is a dependent increase in extraglandular testosterone production. When a woman becomes obese, the conversion of androstenedione to testosterone is increased.

Testosterone is the primary androgen that causes increased hair growth, acne, and the physical changes associated with virilization. After testosterone is secreted, it is bound to a carrier protein — sex hormone-binding globulin (SHBG) — and primarily circulates in plasma as a bound steroid hormone. Bound testosterone is unable to attach to testosterone receptors and is, therefore, metabolically inactive. Only a small fraction (1 to 3 %) of testosterone is unbound (free). This small

fraction of free hormones exerts the effects. The liver produces SHBG. Estrogens stimulate hepatic production of SHBG. Greater estrogen production is associated with less free testosterone, whereas decreased estrogen production is associated with increased free testosterone. Therefore, measurement of total testosterone alone may not reflect the amount of biologically active testosterone.

Testosterone receptors are scattered throughout the body. For the purpose of this discussion, testosterone receptors are considered only in hair follicles, sebaceous glands, and genital skin. Free testosterone enters the cytosol of testosterone-dependent cells. There it is bound to a testosterone receptor and carried into the nucleus of the cell to initiate its metabolic action. Excessive testosterone increases hair growth, acne, and rugation of the genital skin. Some individuals have increased 5α-reductase within hair follicles, resulting in excessive local skin production of DHT.

Excess androgen production has several causes, including polycystic ovarian syndrome, testosterone-secreting tumors, adrenal disorders, and iatrogenic and idiopathic causes.

POLYCYSTIC OVARY SYNDROME

Polycystic ovarian syndrome (PCOS) was described in 1935 by Stein and Leventhal as a syndrome manifested by amenorrhea, hirsutism and obesity associated with enlarged polycystic ovaries.

PCOS is a multifactorial and polygenic condition characterized by excessive androgen production by the ovaries mainly. The etiology of this disorder is unknown. Some cases appear to result from a genetic predisposition, whereas others seem to result from obesity or other causes of LH excess.

Symptoms of PCOS include oligomenorrhea or amenorrhea, acne, hirsutism, and infertility. The disorder is characterized by chronic anovulation or extended periods of infrequent ovulation (oligoovulation). It is a syndrome primarily defined by excess androgen.

According to the Rotterdam consensus workshop the diagnosis is based upon the presence of any two of the following three criteria (ASRM/ESHRE, 2003):

– ovulatory dysfunction — oligo- or anovulation usually marked by irregular menstrual cycles;

– biochemical or clinical evidence of hyperandrogenism;

– polycystic ovarian morphologic features: ovaries are enlarged in volume (> 10 cm^3) or with increased number (> 20) of peripherally arranged antral follicles (2–9 mm) (fig. 5).

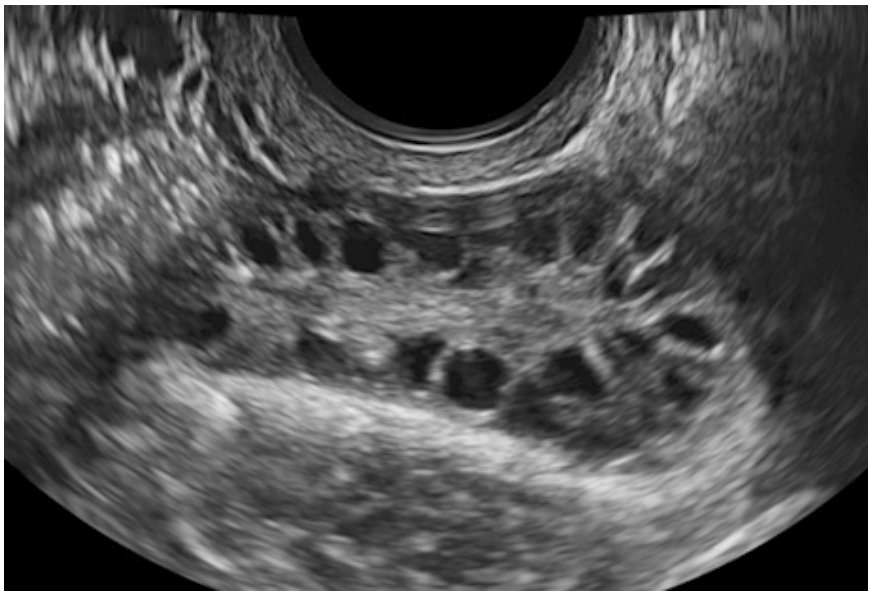

Fig. 5. Polycystic morphology ovaries on ultrasound

It is also important to rule out other endocrine disorders that can mimic PCOS, such as congenital adrenal hyperplasia, Cushing syndrome, and hyperprolactinemia, thyroid dysfunction.

There are 4 phenotypes have been identified as variants of PCOS based on the three key parameters of PCOS, which are anovulation, hyperandrogenism, and polycystic ovaries (table 2).

Table 2

Four major clinical phenotypes of PCOS

Feature	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Biochemical/clinical hyperandrogenism	+	+	+	−
Chronic anovulation	+	+	−	+
Polycystic ovaries	+	−	+	+

Risk factors:

1. Genetics: PCOS is believed to be a complex disorder, with genetic as well as environmental factors contributing to development of the disease. Many pieces of research show that identical twins are more prone to get PCOS than fraternal twins or non-twin siblings. Women having a 50 % chance to get PCOS if their mother or sibling also has this disease. Genes that are linked with PCOS are responsible for the production and metabolism of sex hormones or linked with an impaired function of insulin.

2. Epigenetic (intrauterine exposures): exposures to testosterone in utero may predispose to the later development of PCOS. Animal studies have demonstrated that in utero exposure is correlated with development of a PCOS-like syndrome

including hyperinsulinemia, hyperandrogenism, oligoanovulation, and polycystic ovaries. Exposure to androgens may impair estrogen and progesterone inhibition of GnRH, contributing to increased pulse frequency.

3. Environment/lifestyle: several lifestyle factors and environmental exposures have been associated with a more severe PCOS phenotype. Sedentary lifestyle is associated with increased metabolic dysfunction, and weight gain is associated with oligoanovulation and hyperandrogenism. Environmental androgen-disrupting chemicals may accumulate to a greater extent in individuals with PCOS because of decreased hepatic clearance; these also induce androgen production and insulin resistance.

4. In many women with PCOS, obesity is common factor, and the acquisition of body fat coincides with the onset of PCOS. PCOS is related to obesity by the following mechanism: LH stimulates the theca cells to increase androstenedione production. Androstenedione undergoes aromatization to estrone within adipocytes. Although estrone is a weak estrogen, it has a positive-feedback action or stimulating effect on the pituitary secretion of LH. LH secretion is, therefore, stimulated by increased estrogen. With increasing obesity comes increased conversion of androstenedione to estrone. With the increased rise in androstenedione, there is coincident increased testosterone production, which causes acne and hirsutism.

Therefore, PCOS can be viewed as one of excess androgen and excess estrogen. The unopposed long-term elevated estrogen levels that characterize PCOS increases the risk of abnormal uterine bleeding, endometrial hyperplasia, and, in some cases, the development of endometrial carcinoma.

Irregular menstrual cycles are defined as:

1. Normal in the first year post menarche as part of the pubertal transition.

2. > 1 to < 3 years post menarche: < 21 or > 45 days.

3. > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year.

4. > 1 year post menarche > 90 days for any one cycle.

5. Primary amenorrhea by age 15 or > 3 years post thelarche (breast development).

When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the PCOS Guidelines.

Hormonal studies in women with PCOS show the following:

– increased LH:FSH ratio (over 2 : 1);

– estrone in greater concentration than estradiol;

– androstenedione at the upper limits of normal or increased, DHEA–S may be marginally elevated;

– testosterone at the upper limits of normal or slightly increased;

– SHBG level is reduced.

The typical woman with PCOS has many of the signs of metabolic syndrome (Syndrome X). Approximately 40 % of patients with PCOS have impaired glucose tolerance, and 8 % have overt type 2 diabetes mellitus. These patients should be screened for diabetes mellitus. Classic lipid abnormalities include elevated triglyceride levels, low HDL levels, and elevated LDL levels. Hypertension is also common in individuals. The combination of the preceding abnormalities potentially increases the risk of cardiovascular disease.

Acanthosis nigricans has also been found in a significant percentage of these patients. The HAIR-AN syndrome (hyperandrogenism, insulin resistance, acanthosis nigricans) constitutes a defined subgroup of patients with PCOS. Administration of the insulin-sensitizing agent metformin in these patients also reduces androgen and insulin levels.

Features suggestive of insulin resistance are:

– BMI > 25 kg/m^2;
– Acanthosis nigricans;
– Waist to hip ratio > 0.85.

Pathophysiology. The pathophysiology of this condition is influenced by alterations in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin production, insulin sensitivity, adipose cell activity, inflammatory factors, and sympathetic nerve function (fig. 6).

A. Hypothalamic — pituitary abnormality:

1. Leptin (a peptide, secreted by fat cells and by the ovarian follicle), insulin resistance and hyperandrogenemia are responsible for increased pulse frequency of GnRH and result in increased pulse frequency of LH. GnRH is preferential to LH rather than FSH.

2. Increased pulse frequency and amplitude of LH results in elevated level of LH.

3. FSH level is not increased. This is mainly due to the negative feedback effect of chronically elevated estrogen and the follicular inhibin.

4. Increased free estradiol due to reduced SHBG bears positive feedback relationship to LH.

5. The LH: FSH ratio is increased.

B. Hyperandrogenism. Abnormal regulation of the androgen forming enzyme (P450 C 17) is the main cause for excess production of androgens from the ovaries and adrenals:

1. Ovary produces excess androgens due to — stimulation of theca cells by high LH, P450 C17 enzyme hyperfunction, defective aromatization of androgens to estrogen, stimulation of theca cells by IGF-1 (insulin growth factor-1).

2. Adrenals are stimulated to produce excess androgens by stress, P450 C17 enzyme hyperfunction, related high prolactin level.

C. Metabolic changes:

1. Hyperinsulinemia results in stimulation of theca cells to produce androgens, increases free IGF-1 level, which stimulates theca cells to produce more androgens, inhibits hepatic synthesis of SHBG, resulting in more free level of androgens.

2. Hyperprolactinemia associated with increased pulsitivity of GnRH or due to dopamine deficiency or both induces adrenal androgen production.

D. Ovulatory disfunction. Follicular growth is arrested at different phases of maturation due to low FSH level what contributes diminished estradiol and increased inhibin production. Elevated LH leads to hypertrophy of theca cells and hyperandrogenism. Follicular growth, maturation and ovulation cannot occur. There is huge number of atretic follicles that contribute to increased ovarian stroma (hyperthecosis).

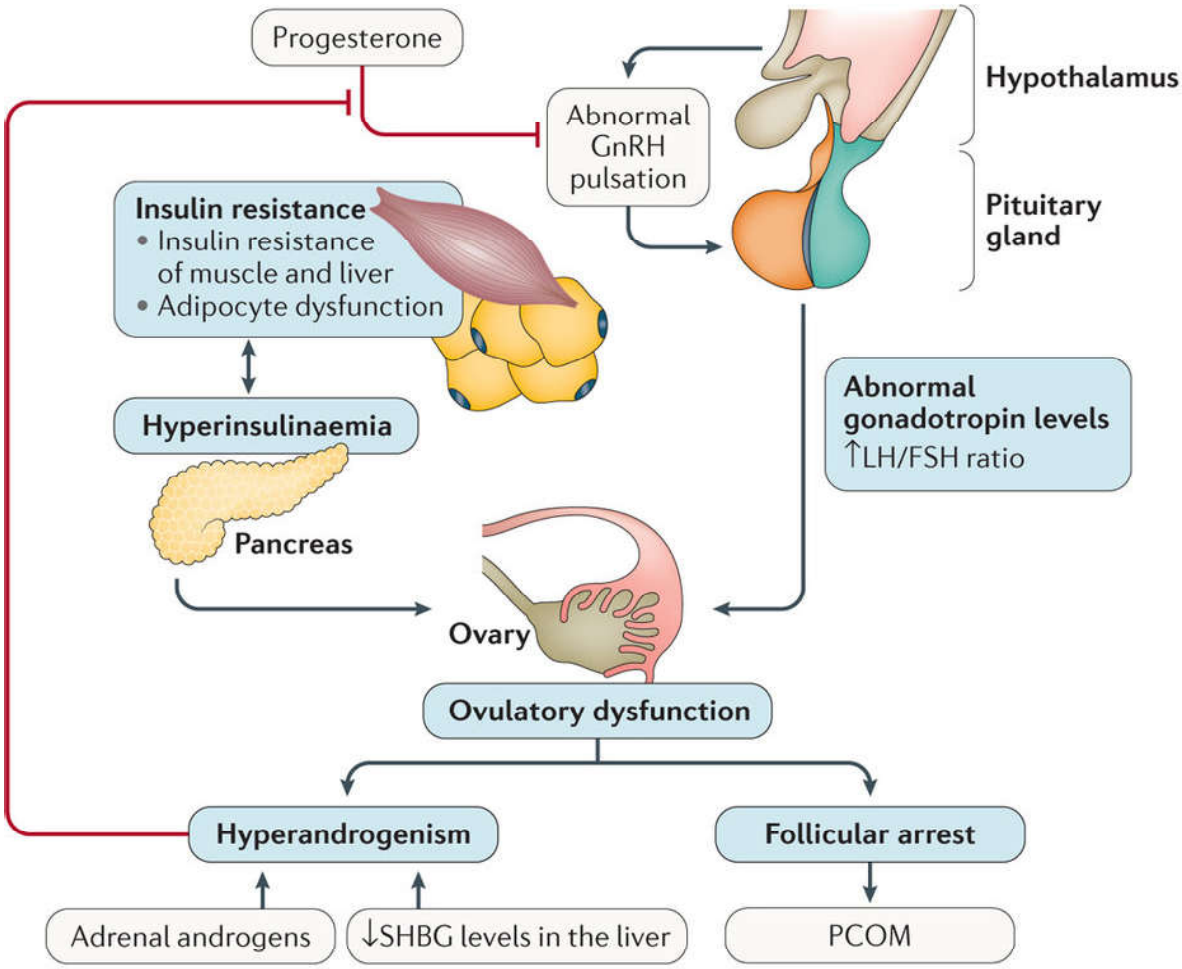

Fig. 6. Pathophysiology of PCOS

Comorbidities of PCOS:

1. Subfertility is a consequence of oligoanovulation, but may also result from abnormalities in oocyte development and endometrial pathology due to hormonal or other abnormalities.

2. Miscarriage: there is an increased risk of miscarriage in PCOS patients who do conceive; however, this risk is confounded by the high rate of obesity in this population, which is also a risk factor for miscarriage.

3. Cardiovascular disease: patients with PCOS often exhibit dyslipidemia, which is likely related both to hyperinsulinemia and hyperandrogenism.

4. Diabetes mellitus type 2: patients with PCOS are thought to have an increased risk of developing type 2 diabetes mellitus above the risk conferred by their level of insulin resistance.

5. Malignancies: a combination of hyperinsulinemia, hyperandrogenism, and oligoanovulation increases the risk of endometrial cancer and other endometrial disorders.

6. Psychiatric disorders: women with PCOS have an increased risk of anxiety, depression, binge-eating disorder, and bipolar disorder.

Management. Lifestyle modification may help attenuate all symptoms of PCOS and reduce the long-term risks of infertility, CVD and carbohydrate intolerance. This is the first line of PCOS management. Increased exercise, improved diet, and weight loss can help to reduce the metabolic abnormalities associated with PCOS. Weight loss of as little as 5–10 % has been demonstrated to correct oligoanovulation and improve the ability of women with PCOS to conceive.

The most common therapy for PCOS is the administration of combined oral contraceptives, which suppresses pituitary LH production. Suppressing LH causes decreased production of androstenedione and testosterone. The ovarian contribution to the total androgen pool is thereby decreased. Acne clears, new hair growth is prevented, and there is decreased androgenic stimulation of existing hair follicles. By preventing estrogen excess, oral contraceptives also prevent endometrial hyperplasia, and women have cyclic, predictable, withdrawal bleeding episodes.

If a woman with PCOS wishes to conceive, oral contraceptive therapy is not a suitable choice. If the patient is obese, a weight-reduction diet designed to restore the patient to a normal weight should be encouraged. With body weight reduction alone, many women resume regular ovulatory cycles and conceive spontaneously.

Controlled induction of ovulation achieves with clomiphene citrate and is facilitated by weight reduction. Clomiphene citrate is a selective estrogen receptor modulator. It induces ovulation by interfering with estrogen feedback to the brain and thus increasing FSH release. There is increased risk of multigestational pregnancy (e. g. twins or triplets) because of the large number of antral follicles in polycystic ovaries. Furthermore, although most women will ovulate on clomiphene

citrate, only half will actually conceive. This may be related to the anti-estrogenic effects of clomiphene, which can result in thinning of the endometrium. Clomiphene citrate treatment should be limited to 12 cycles because longer-term treatment is associated with increased risk of ovarian cancer due to ovarian hyperstimulation. First line of induction of ovulation is antiestrogens — Letrozole.

Insulin sensitizers (metformin) alone or with clomiphene citrate may be used to reduce insulin resistance, control weight, and facilitate ovulation. Metformin reduces glucose intolerance and hyperinsulinemia by increasing insulin sensitivity and decreasing hepatic gluconeogenesis and lipogenesis.

Gonadotropin therapy: recombinant FSH and human chorionic gonadotropin can be used to induce ovulation in cases where treatment with clomiphene citrate and metformin has been unsuccessful. Exogenous gonadoptropins can be administered to mimic physiological mechanisms of follicle development. FSH is given to promote growth of a dominant follicle to a particular size, and then human chorionic gonadotropin is used to induce ovulation. This therapy must be closely monitored with imaging and laboratory studies to minimize the risks of multigestational pregnancy and ovarian hyperstimulation.

Laparoscopic ovarian surgery is second line therapy for women with PCOS who are anovulatory and infertile with clomiphene citrate resistance and no other infertility factors. Ovarian drilling: a laparoscopic surgical procedure that may be used to treat clomiphene citrate-resistant anovulation. Ovarian drilling involves the creation of 10 perforations in the ovary using either cautery or laser. The ablation of some of the ovarian theca is thought to help induce ovulation by decreasing androgen production. This procedure may have similar efficacy to gonadotropin therapy, but surgical complications such as adhesion formation remain a concern. This procedure is especially useful in patients with other existing indications for laparoscopy.

Hyperthecosis is a more severe type of PCOS. In cases of hyperthecosis, androstenedione production significantly increase and testosterone reaches concentrations that cause virilization. Women with this condition may exhibit temporal balding, clitoral enlargement, deepening of the voice, and remodeling at the limb–shoulder girdle. Hyperthecosis is often refractory to oral contraceptive suppression. It is also more difficult to successfully induce ovulation in women with this condition.

Anti-androgens (e. g. spironolactone, finasteride, flutamide) is effective for treatment of acne and hirsutism. Spironolactone and flutamide competitively inhibits DHT and testosterone by binding to their receptors in peripheral cells (e. g. hair follicles). Finasteride is a 5a-reductase inhibitor that inhibits conversion of testosterone to the more potent DHT in peripheral cells. Anti-androgens can be used synergistically with OCPs, which act centrally to suppress androgen release. Note that anti-androgens are contraindicated in pregnancies because they are teratogens.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders that arise from defective steroidogenesis caused by enzyme deficiencies that result in precursor (substrate) excess, thus resulting in androgen excess. DHEA is a precursor for androstenedione and testosterone.

Adrenal steroidogenesis occurs in three major pathways: glucocorticoids, mineralocorticoids, and sex steroids (fig. 7). Glucocorticoids (particularly cortisol), androgens, and estrogens are synthesized in the zona fasciculata and reticularis; and aldosterone in the zona glomerulosa. The hypothalamo-pituitary-adrenal feedback system is mediated through the circulating level of plasma cortisol by negative feedback of cortisol on corticotropin-releasing factor and ACTH secretion. Therefore, a decrease in cortisol secretion leads to increased ACTH production, which in turn stimulates (1) excessive synthesis of adrenal products in those pathways unimpaired by the enzyme deficiency and (2) an increase of precursor molecules in pathways blocked by the enzyme deficiency.

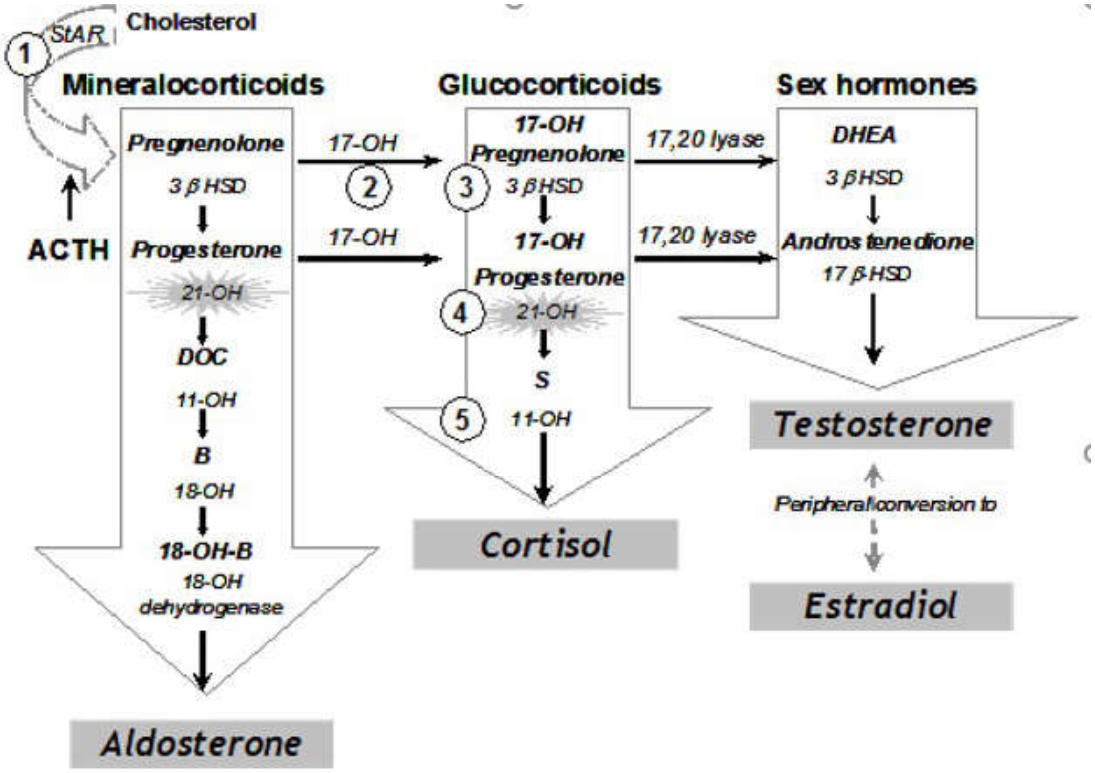

Fig. 7. Pathways of Adrenal Steroidogenesis: Five enzymatic steps necessary for cortisol production are shown in numbers. 1 = 20, 22 desmolase, 2 = 17 hydroxylase (17-OH), 3 = 3ß-hydroxysteroid dehydrogenase (3ß HSD), 4 = 21 hydroxylase (21-OHD), 5 = 311ß hydroxylase (11-OH). In the first step of adrenal steroidogenesis, cholesterol enters mitochondria via a carrier protein called StAR. ACTH stimulates cholesterol cleavage, the rate limiting step of adrenal steroidogenesis

The clinical symptoms of the five different forms of CAH result from the particular hormones that are deficient and those that are produced in excess.

When 21-hydroxylase is deficient, there is an accumulation of progesterone and 17α-hydroxyprogesterone, which are metabolized subsequently to DHEA. This disorder affects approximately 2 % of the population and is caused by an alteration in the genes for 21-hydroxylase, which are carried on chromosome 6. The genetic defect is autosomal recessive and has variable penetrance.

In the most severe form of 21-hydroxylase deficiency, the newly born female infant is simply virilized (ambiguous genitalia) or is virilized and suffers from life-threatening salt wasting.

Clinical features of 21-Hydrolase Deficiency. Females with Classical 21-hydroxylase and 11β-hydroxylase deficiency CAH present at birth with virilization of their genitalia. Adrenocortical function begins around the 7th week of gestation; thus, a female fetus with classical CAH is exposed to adrenal androgens at the critical time of sexual differentiation (approximately 9 to 15 weeks gestational age). This leads to clitoral enlargement, fusion and scrotalization of the labial folds, and rostral migration of the urethral/vaginal perineal orifice, placing the phallus in the male position. Internal female genitalia, such as the uterus, fallopian tubes and ovaries, develop normally. Females with classical CAH maintain the internal genitalia potential for fertility.

Severe:

1. Newborn female infant is virilized (ambiguous genitalia), or virilized.
2. Adrenal aldosterone secretion is not sufficient for sodium reabsorption by the distal renal tubules, and individuals suffer from salt wasting as well as cortisol deficiency and androgen excess.
3. Infants with renal salt wasting have poor feeding, weight loss, failure to thrive, vomiting, dehydration, hypotension, hyponatremia, and hyperkalemic metabolic acidosis progressing to adrenal crisis (azotemia, vascular collapse, shock, and death).
4. Adrenal crisis can occur as early as age one to four weeks.

Mild:

1. This type is frequently associated with terminal body hair, acne, alopecia, subtle alterations in menstrual cycles and infertility.
2. Patients can also have sonographic evidence of polycystic-appearing ovaries.
3. Manifested at puberty.
4. Adrenarche may precede thelarche.
5. History of pubic hair growth occurring before the onset of breast development may be a clinical clue.

Diagnosis. The diagnosis of 21-hydroxylase deficiency is based on measuring increased 17-OH progesterone in plasma during the follicular phase (preferably

measured while fasting). Patients with classic 21-hydroxylase deficiency will have significantly elevated plasma 17-OH progesterone levels, usually over 2000 ng/dL. Those with less severe 21-hydroxylase deficiency may have mildly elevated basal levels, 200 ng/dL. False negative results may occur if samples are drawn late in the afternoon as adrenal hormones exhibit diurnal variation. DHEA-S and androstenedione will also be elevated and contribute to the hirsutism and virilizing signs.

The gold standard for hormonal diagnosis is the corticotropin stimulation test (250 μg cosyntropin intravenously), measuring levels of 17-OH and androstenedione at baseline and 60 min. These values can then be plotted in the published nomogram to ascertain disease severity. The corticotropin stimulation test should not be performed during the initial 24 hours of life as samples from this period are typically elevated in all infants and may yield false-positive results. Establishing a genetic diagnosis is not only important for the genotype-phenotype correlation, but also for genetic counseling for future pregnancies and for genetic counseling for the patient and his/her reproductive future.

For 21-hydroxylase deficiency CAH, genetic analysis of the CYP21A2 gene may provide more clues to predict phenotypic severity. In about 50 % of the causative genotypes, genotype-phenotype correlation can be found, although certain mutations can lead to variable phenotypes in different population groups especially in the simple virilizer group. Sequencing of the entire gene should be performed to detect rare mutations when genotype–phenotype non-concordance is observed in patients with CAH.

A less-common cause of adrenal hyperplasia is 11β-hydroxylase deficiency. The enzyme 11β-hydroxylase catalyzes the conversion of desoxycorticosterone to cortisol. A deficiency in this enzyme also results in increased androgen production. The clinical features of 11β-hydroxylase deficiency are mild hypertension and mild hirsutism. The diagnosis of 11β-hydroxylase deficiency is made by demonstrating increased plasma desoxycorticosterone.

Treatment. The goal of therapy in CAH is to both correct the deficiency in cortisol secretion and to suppress ACTH overproduction. Proper treatment with glucocorticoid reduces stimulation of the androgen pathway, thus preventing further virilization and allowing normal growth and development. A small dose of dexamethasone at bedtime (0.25 to 0.5 mg) is usually adequate for androgen suppression in non-classical adult patients. Adequate biochemical control is assessed by measuring serum levels 17-OH and androstenedione; serum testosterone can be used in females and prepubertal males (but not newborn males). Usually, prednisone, 2.5 mg daily (or its equivalent), suppresses adrenal androgen production to within the normal range. When this therapy is instituted, facial acne usually clears promptly, ovulation is restored, and there is no new terminal hair growth.

Medical therapy for adrenal and ovarian disorders cannot resolve hirsutism. It can only suppress new hair growth. Hair that is present must be controlled by shaving, bleaching, using depilatory agents, by electrolysis or laser hair ablation.

Cushing Syndrome. Cushing syndrome is an adrenal disease resulting in adrenal excess. As a result of an adrenal neoplasm or an ACTH-producing tumor, the patient demonstrates signs of corticosteroid excess that include truncal obesity, moonlike facies, glucose intolerance, skin thinning with osteoporosis, proximal muscle weakness in addition to evidence of hyperandrogenism, and menstrual irregularities.

Adrenal Neoplasms. Androgen-secreting adrenal adenomas cause a rapid increase in hair growth associated with severe acne, amenorrhea, and sometimes virilization. In androgen-secreting adenomas, DHEA-S is usually elevated above 6 mg/mL. The diagnosis of this rare tumor is established by computed axial tomography or magnetic resonance imaging of the adrenal glands. Adrenal adenomas must be removed surgically.

CONSTITUTIONAL HIRSUTISM

Occasionally after a diagnostic evaluation for hirsutism, there is no explanation for the cause of the disorder. By exclusion, this condition is often called constitutional hirsutism. Data support the hypothesis that women with con- stitutional hirsutism have greater activity of 5α-reductase than do unaffected women.

Treatment of constitutional hirsutism is primarily androgen blockade and mechanical removal of the excess hair. Spironolactone 100 mg/day is the most commonly used androgen blocker. Spironolactone also inhibits testosterone production by the ovary and reduces 5α-reductase activity. Other androgen blockers include flutamide and cyproterone acetate. The activity of 5α-reductase can also be inhibited directly through the use of drugs such as finasteride (5 mg orally daily). Eflornithine hydrochloride 13.9 % is an irreversible inhibitor of L-ornithine decarboxylase, which slows and shrinks hair. This cream has been approved for facial use with satisfactory local effects.

Patients taking an androgen receptor or 5α-reductase blocker should be placed on concomitant oral contraceptives because of the teratogenic and demasculinizing effects on a fetus should pregnancy occur. Oral contraceptives may also improve the efficacy of these treatments through the decreased androgen and increased SHBG production effects associated with their use.

IATROGENIC ANDROGEN EXCESS

Some drugs with androgen activity have been implicated in hirsutism and virilization, including danazol and progestin- containing oral contraceptives.

Danazol is an attenuated androgen used for the suppression of pelvic endometriosis. It has androgenic properties, and some women develop hirsutism, acne, and deepening of the voice while taking the drug. If these symptoms occur, the value of the danazol should be weighed against the side effects before continuing therapy. Symptoms of voice changes may be irreversible upon discontinuation of treatment. Pregnancy should be ruled out before initiating a course of danazol therapy, because it can produce virilization of the female fetus.

Oral Contraceptives: the progestins in oral contraceptives are impeded androgens. Rarely, a woman taking oral contraceptives develops acne and even hirsutism. If this occurs, another product with a less-androgenic progestin should be selected, or the pill should be discontinued. Moreover, evaluation for the coincidental development of late-onset adrenal hyperplasia should be done.

SELF-CONTROL

Situational tasks

Task 1

A 35-year-old woman presents to her general practitioner with cyclical labile mood swings that occurred during last 6 months. She complained on having also weight gain, breast tenderness, headaches, swelling and abdominal bloating. She reports her periods as always having been painful and that she has always been irritable and suffering approximately a week to a menstruation. However now she feels that she is not herself for at least 2 weeks before her menstruation and that the pain has worsened. Her menstrual cycle is regular (every 30–31 days). She has had 2 children by normal vaginal delivery. She has no other medical history. She is married for 10 years and often feels aggressive towards her husband or alternatively is tearful.

Examination: No abnormality is found on abdominal or neurological examination. Blood pressure is 120/80 mmHg.

Questions:

1. What is diagnosis?
2. What disorders are for the differential diagnosis?
3. What is the most effective management of this patient?

Task 2

A 20-year-old woman presents with a complaint of increased hair growth.

She first noticed the problem when she was about 15–16 years old and it has progressively worsened such that she now feels very self-conscious and will never wear a bikini or go swimming. The hair growth is noticed mainly on her arms, thighs and abdomen. Hair has developed on the upper lip more recently.

There is no significant previous medical history of note. Her periods started at the age of 13 years and menstrual cycle is 30–42 days. The periods are not painful or heavy and there is no intermenstrual bleeding or discharge. She has never been sexually active.

On examination she has an increased body mass index (BMI) of 30 kg/m^2. The blood pressure is 120/70 mmHg. There is excessive hair growth on the lower arms, legs and thighs and in the midline of the abdomen below the umbilicus. There is a small amount of growth on the upper lip too. The abdomen is soft and no masses are palpable. Pelvic examination is not indicated as she is a virgin.

Hormonal assay at 4th day of menstrual cycle: FSH 5,6 IU/L, LH 16.2 IU/L, Prolactin 511 mU/L, TSH 3.2 mU/L, free thyroxine 12.7 nmol/L, testosterone total 3.2 nmol/L, SHBG 21 nmol/L.

Questions:

1. What is the likely diagnosis?
2. How would you further investigate and manage this woman?

Task 3

A 35-year-old woman complains of missing of a menstruation for 3 months. Pregnancy tests have been negative. She started her periods at the age of 15 years and until 33 years she had a normal 30-day cycle. She had one normal delivery 2 years ago. After that she had normal cycles for several months and then her periods stopped abruptly. She was using the progesterone only pill for contraception while she was breast-feeding and stopped 6 months ago as she is keen to have another child. She reports symptoms of dryness during intercourse and has experienced sweating episodes at night as well as episodes of feeling extremely hot at any time of day. There is no relevant gynaecological history. The only medical history of note is hypothyroidism for 10 years and takes thyroxine 100 pig per day. She does not take any alcohol, smoke or use drugs.

Examination: Examination findings are unremarkable.

Hormonal investigation: TSH 3.2 mU/L, Free thyroxine 16.2 pmol/L, FSH 55 IU/L, LH 35 IU/L, Prolactin 401 mU/L, Estradiol 87 pmol/L, Testosterone 2.3 nmol/L.

Questions:

1. What is the diagnosis?
2. What further investigations should be performed?
3. What are the important points in the management of this woman?

Answers

Task 1

The diagnosis is premenstrual syndrome.

The diagnosis is confirmed with symptoms occurring in the luteal phase and resolving within a day of menstruation starting.

The differential diagnosis is depression which can manifest in a similar way to PMS.

A symptom diary should be recorded for each day, over a 3-month period, which annotate the severity of each symptom and when menstruation occurs. PMS should start after midcycle, symptoms should resolve with the menstruation, and there should be a number of symptom-free days each month.

Task 2

The likely diagnosis is polycystic ovarian syndrome (PCOS), which confirmed by the clinical features of hirsutism, acne, increased BMI and slight menstrual irregularity. The hormonal results show the typical moderately raised testosterone and raised LH to FSH ratio.

A transabdominal ultrasound scan should be performed to confirm the ultrasound features of polycystic ovaries. Assessment of glucose metabolism: glucose, insulin, leptin, glycosilated hemoglobin.

Targeted treatment should be performed for women with PCOS. The leading sign is hirsutism. One of the commonest is to commence the cyproterone acetate-containing combined oral contraceptive pill. Cyproterone acetate is an anti-androgen with progestogenic activity. It takes several months for an improvement to be seen in the hair growth and she will continue to need to use the cosmetic treatments in the meantime.Also possible anti androgen effect might be achieved by using spironolactone (100 mg per day).

General advice should include modifying life style, weight loss, as this counteracts the metabolic imbalance associated with PCOS.

Task 3

Symptoms of amenorrhoea, vasomotor symptoms and vaginal dryness are related to diagnosis of premature menopause. It is confirmed by the high gonadotrophin levels.

Management: Osteoporosis may be prevented with ostrogen replacement, with progesterone protection of the uterus. Traditional cyclic HRT preparations are effective.

Tests

1. **What criteria includes the diagnosis of PCOS:**
   a) amenorrhea;
   b) uterine infantilism;
   c) biochemical or clinical hyperandrogenism;
   d) ovarian cysts;
   e) infertility.

2. **What clinical sign is not characterized for PCOS:**
   a) chronic anovulation;
   b) hirsutism;
   c) infertility;
   d) mastalgia;
   e) oligomenorrhea.

3. **What is the most potent androgen:**
   a) testosterone;
   b) dehydroandrostendion;
   c) androstenedione;
   d) dehydrotestosteron;
   e) 17-hydro progesterone.

4. **What hormonal studies don't show in women with PCOS :**
   a) LH:FSH ratio over 2.5;
   b) FSH:LH ratio over 2.5;
   c) androstenedione at the upper limits of normal or increased;
   d) testosterone at the upper limits of normal or slightly increased;
   e) estron is dominating by estradiol.

5. **What is the first-line therapy for women with PCOS**
   a) GnRH agonists;
   b) combined oral contraceptives;
   c) progestins;
   d) dophamin agonists;
   e) antiandrogens.

6. **What medicine is not used for induction of ovulation in pcos patients**
   a) letrozole;
   b) clomiphene citrate;
   c) pure FSH;
   d) human menopausal gonadotropins;
   e) estrogens.

7. What menstrual cycle abnormalities in perimenopause are not common

a) abrupt cessation of menstruation;
b) gradual decrease in amount;
c) irregular menstruation with excessive bleeding;
d) painful menstruations;
e) none above.

8. What is intermediate sign of menopause

a) hot flashes;
b) depression;
c) vaginal atrophy and frequent urination;
d) cardiovascular disorders;
e) osteoporosis.

9. What sign is not associated with premenstrual syndrome

a) abdominal bloating;
b) breast tenderness;
c) weight loss;
d) depression;
e) insomnia.

10. All above are risks of HRT except

a) breast cancer;
b) endometrial cancer;
c) cardiovascular disease;
d) lipid metabolic disturbance;
e) osteoporosis.

Answers: 1 — c; **2** — d; **3** — d; **4** — b; **5** — b; **6** — e; **7** — d; **8** — c; **9** — c; **10** — c.

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CONTENT

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