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НЕЙРОЭНДОКРИННЫЕ СИНДРОМЫ В ГИНЕКОЛОГИИ

Учебно-методическое пособие на английском языке
для студентов 5 и 6 курсов факультета по подготовке специалистов
для зарубежных стран медицинских вузов

NEUROENDOCRINE SYNDROMS IN GYNECOLOGY

Teaching workbook in English
for 5th and 6th year students
of the Faculty on preparation of experts for foreign countries
of medical highest educational institutions

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В учебно-методическом пособии рассматриваются вопросы диагностики и лечения нейроэндокринных синдромов в гинекологии. Соответствует учебному плану и программе для студентов медицинских вузов Министерства здравоохранения Республики Беларусь.

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ABBREVIATIONS

ACTH — Adrenocorticotropic hormone

CT — Computerized tomography

DHEA-S — Dehydroepiandrosterone sulfate

GnRH — Gonadotropin-releasing hormone

HRT — Hormone Replacement Therapy

FSH — Follicle stimulating hormone

IGF-1 — Insulin growth factor-1

LDL — Low density lipoprotein

LH — Luteinizing hormone

MRI — Magnetic resonance imaging

PCOS — Polycystic ovarian syndrome

PMS — Premenstrual syndrome

SERMs — Selective estrogen receptor modulators

SHBG — Sex hormone binding globulin

TSH —Thyroid-stimulating hormone

PREMENSTRUAL SYNDROME

Premenstrual syndrome is a psychoneuroendocrine 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. It should fulfil the following criteria:

- 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.

Pathophysiology. The exact cause is not known but the following hypotheses are postulated:

- Alteration in the level of estrogen and progesterone starting from the mid-luteal phase.
- Neuroendocrine factors. During the luteal phase, decreased synthesis of serotonin is observed in women suffering from PMS. The symptom complex of PMS is thought to be due to the withdrawal of endorphins during the luteal phase.
- Psychological and psychosocial factors may be involved to produce behavioral changes.

Symptoms:

1. Related to water retention: breast tenderness, weight gain.

2. Neuropsychiatric symptoms: irritability, depression, mood swings, anxiety.

3. Behavioral symptoms: dyspareunia, insomnia.

Clinical features: PMS is more common in women aged 30–45. It may be related to childbirth or a disturbing life event. There are no abnormal pelvic findings excepting features of pelvic congestion.

Treatment: As the etiology is multifactorial and too often obscure, various drugs are used.

1. Nonpharmacological: diet manipulation, avoidance of salt, caffeine and alcohol specially in second half of cycle. Life style modification and congnitive behavior therapy.

2. Nonhormonal: tranquilizers or antidepressant drugs, Pyridoxine — 100 mg twice daily, diuretics in the second half of the cycle.

3. Hormones: oral contraceptive pills. The idea is to suppress ovulation and to maintain an uniform hormonal level. The therapy is to be continued for 3–6 cycles. Newer oral contraceptive pills contain progestin drospirenone. It has antimineralocorticoid and antiandrogenic properties. Progesterone is not effective in treating PMS.

CLIMACTERIC SYNDROM

Menopause means permanent cessation of menstruation at the end of reproductive life due to loss of ovarian follicular activity. It is the point of time when last and final menstruation occurs.

The clinical diagnosis is confirmed following stoppage of menstruation (amenorrhea) for twelve consecutive months without any other pathology. As such, a woman is declared to have attained menopause only retrospectively.

Premenopause — period prior to menopause.

Postmenopause — period after menopause,

Perimenopause — period around menopause (40–55 years).

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

Age at which menopause occurs is genetically predetermined. The age of menopause is not related to age of menarche or age at last pregnancy. However, cigarette smoking and severe malnutrition may cause early menopause. The age of menopause ranges between 45–55 years, average being 50 years.

Endocrinology of climacteric and menopause

1. Hypothalamopituitary gonadal axis. Few years prior to menopause, the follicles become resistant to pituitary gonadotropins. There is a significant fall in the level of serum estradiol. This decreases the negative feedback effect on hypothalamopituitary axis resulting in increase in FSH.

Disturbed folliculogenesis during this period may result in anovulation, oligoovulation, corpus luteal insufficiency. The sustained level of estrogens may even cause endometrial hyperplasia and clinical manifestation of menstrual abnormalities prior to menopause. The mean cycle length is significantly shorter. This is due to shortening of the follicular phase of the cycle. Luteal phase's length remains constant. Ultimately, no more follicles are available and even some exist, they are resistant to gonadotropins.

2. Estrogens. Following menopause, the predominant estrogen is estrone and to a lesser extent estradiol. Serum level of estrone is higher than that of estradiol. The major source of estrone is peripheral conversion of androgens from adrenals and ovaries. The aromatization occurs at the level of muscle and adipose tissue. The trace amount of estradiol is derived from peripheral conversion of estrone and androgens. Compared to estradiol, estrone is biologically less potent. With times, the sources fail to supply the precursors of estrogen and about 5–10 years after menopause, there is a sharp fall in estrogen and also the trophic hormones. The woman is said to be in a state of true menopause.

3. Androgens. After menopause, the stromal cells of the ovary continue to produce androgens because of increase in LH. The main androgens are androstenedione and testosterone. It results in 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.

4. Progesterone: A trace amount of progesterone detected is probably adrenal in origin.

5. Gonadotropins. The secretions of both FSH and LH are increased due to absent negative feedback effect of estradiol and inhibin or due to enhanced responsiveness of pituitary to GnRH.

Organ changes. Ovaries shrink in size, become wrinkled and white. The uterus becomes smaller, the endometrium becomes thin and atrophic. The vagina becomes narrower due to gradual loss of elasticity. The vaginal epithelium becomes thin. The vaginal pH becomes alkaline. There is no glycogen. Doderlein's bacillus is absent. The vaginal pH becomes alkaline. Bladder and urethra undergo similar changes to those of the vagina. The epithelium becomes thin and is more prone to damage and infection. There may be dysuria, frequency, urge or even stress incontinence. Loss of muscle tone leads to pelvic relaxation, uterine descent and anatomic changes in the urethra and neck of the bladder. The pelvic cellular tissues become scanty and the ligaments supporting the uterus and vagina lose their tone. As such preexisting weakness gets aggravated.

Symptoms of menopause:

1. Vasomotor symptoms: The characteristic symptom of menopause is «hot flush». Hot flush is characterized by sudden feeling of heat followed by profuse sweating. It may last for 1–10 minutes, and may be at times unbearable. Sleep may be disturbed due to night sweats.

2. Genital and urinary system: Estrogen plays an important role to maintain the epithelium of vagina, urinary bladder and the urethra. Estrogen deficiency produces atrophic epithelial changes in these organs. This may cause dyspareunia and dysuria (urethral syndrome). The weakness of the supporting muscles and the cardinal ligaments allows stress incontinence to start at this age.

3. Skin and hair: There is thinning, loss of elasticity and wrinkling of the skin. Skin collagen content and thickness decrease by 1–2 % per year.

4. Psychological changes: There is increased frequency of anxiety, headache, insomnia, depression. They also suffer from dementia, mood swing and inability to concentrate. Estrogen increases neurotransmitter activity in the brain and is known to be important for memory.

5. Dementia: Estrogen is thought to protect the function of central nervous system. Dementia and mainly Alzheimer disease are more common in postmenopausal women.

6. Osteoporosis: 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 and in cortical bones. Bone loss increases to 5% per year during menopause.

Treatment.

1. Nonhormonal treatment.
2. Hormone replacement therapy.

NONHORMONAL TREATMENT

• **Lifestyle modification**. Physical activity, reducing high coffee intake, smoking and excessive alcohol. Nutritious diet — balanced with calcium and protein is helpful, supplementary calcium — daily intake of 1–1,5 g can reduce osteoporosis and fracture. Women should be monitored with bone density measurement. Alendronate, ibandronate and zolendronic acid are also effective and have less side effects.

• **Selective estrogen receptor modulators** (SERMs) are tissue specific in action. Of the many SERMs, raloxifene has shown to increase bone mineral density. 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.

• **Selective serotonin reuptake inhibitor,** is effective to reduce hot flushes (both the frequency and severity).An analog of gamma-aminobutyric acid is effective to control hot flushes.

• **Phytoestrogens** containing isoflavones are found to lower the incidence of vasomotor symptoms, osteoporosis and cardiovascular disease. It reduces the risk of breast and endometrial cancer. It acts as SERMS.

HORMONE REPLACEMENT THERAPY

The hormone replacement therapy (HRT) is indicated in menopausal women to overcome the short-term and long-term consequences of estrogen deficiency. Indication of HRT: relief of menopausal symptoms, prevention of osteoporosis, to maintain the quality of life in menopause.

HRT prevents bone loss and stimulate new bone formation. HRT reduces the risk of vertebral and hip fracture (25–50 %). Estrogen is found to play a direct role, as receptors have been found in the osteoblasts. Women receiving HRT should supplement their diet with an extra 500 mg of calcium daily. Total daily requirement of calcium in postmenopausal women is 1.5 g. HRT is thought to be cardiovascular protective. Estrogen prevents oxidation of LDL, as it has got antioxidant properties. In postmenopausal women, there is some amount of insulin resistance and hyperinsulinemia, which induces atherogenesis.

Risks of hormone replacement therapy:

1. Endometrial cancer. When estrogen is given alone to a woman with intact uterus, it causes endometrial proliferation, hyperplasia and carcinoma. It is therefore advised that a progestogen should be added to ERT to counter balance such risks.

2. Breast cancer. Combined estrogen and progestin replacement therapy, increases the risk of breast cancer slightly. Adverse effects of hormone therapy are related to the dose and duration of therapy.

3. Venous thromboembolic disease has been found to be increased with the use of combined oral estrogen and progestin.

4. Lipid metabolism. An increased incidence of gallbladder disease has been observed following ERT due to rise in cholesterol.

Benefits of hormone replacement therapy:

1. Improvement of vasomotor symptoms.
2. Improvement urogenital atrophy.
3. Increase in bone mineral density.
4. Decreased risk in vertebral and hip fractures.
5. Reduction in colorectal cancer.
6. Cardioprotection.

Available preparations for hormone replacement therapy. The principal hormone used in HRT is estrogen. This is ideal for a woman who had her uterus removed (hysterectomy) already. But in a woman with an intact uterus, only estrogen therapy leads to endometrial hyperplasia and even endometrial carcinoma. Addition of progestins for last 12–14 days each month can prevent this problem.

Generally, use of HRT for a short period of 3–5 years has been advised. Reduction of dosage should be done as soon as possible.

Considering the risks, hormone therapy should be used with the lowest effective dose and for a short period of time. Low dose oral conjugated estrogen 0.3 mg daily is effective and has got minimal side effects. Dose interval may be modified as daily for initial 2–3 months then it may be changed to every other day for another 2–3 months and then every third day for the next 2–3 months. It may be stopped thereafter if symptoms are controlled.

Oral estrogen regime. Estrogen — conjugated equine estrogen s given daily for woman who had hysterectomy.

Estrogen and cyclic progestin. For a woman with intact uterus estrogen is given continuously for 25 days and progestin is added for last 12–14 days.

Continuous estrogen and progestin therapy. Continued combined therapy can prevent endometrial hyperplasia. There may be irregular bleeding with this regimen.

Subdermal implants. Implants are inserted subcutaneously over the anterior abdominal wall using local anesthesia and can be kept for 6 months. This method is suitable in patients after hysterectomy.

Percutaneous estrogen gel. 1 g applicator of gel is to be applied onto the skin over the anterior abdominal wall or thighs.

Transdermal patch. It should be applied below the waist line and changed twice a week. Skin reaction, irritation and itching have been noted with their use.

Vaginal cream. Conjugated equine vaginal estrogen is very effective specially when associated with atrophic vaginitis. Women with symptoms of urogenital atrophy and urinary symptoms and who do not like to have systemic HRT, are suitable for such treatment.

Progestins. In patients with history of breast carcinoma, or endometrial carcinoma, progestins may be used. It may be effective in suppressing hot flushes and it prevents osteoporosis.

Tibolone. Tibolone is a steroid (19-nortestosterone derivative) having weakly estrogenic, progestogenic and androgenic properties. It prevents osteoporosis, atrophic changes of vagina and hot flushes.

Generally, use of HRT for a short period of 3–5 years have been advised. Reduction of dosage should be done as soon as possible. Menopausal women should maintain optimum nutrition, ideal body weight and perform regular exercise.

SYNDROME AFTER TOTAL OOPHORECTOMY

Syndrome after total oophorectomy is artificial menopause induced by surgery (bilateral oophorectomy) or by radiation during reproductive period.

Artificial Menopause. Permanent cessation of ovarian function done by artificial means, e.g. surgical removal of ovaries or by radiation is called artificial menopause.

Surgical Menopause. Menstruating women who have bilateral oophorectomy, experience menopausal symptoms (see climacteric symptom). It is sometimes more troublesome than natural menopause.

Radiation Menopause: The ovarian function may be suppressed by external gamma radiation in women below the age of 40. The castration is not permanent. The menstruation may resume after 2 years and even conception is possible. Intracavity introduction of radium can cause castration effect by destroying the endometrium and also by depressing the ovarian function. The menopausal symptoms are not so intense as found in surgical menopause or menopause following external radiation.

Treatment. Hormone replacement therapy (see climacteric symptom).

ADRENOGENITAL SYNDROME (CONGENITAL ADRENAL HYPERPLASIA)

Etiology. It is an autosomal recessive disorders due to inborn error of adrenal steroid metabolism, commonly due to 21-hydroxylase (95%) and rarely due to 11-hydroxylase or 3β-hydroxy steroid dehydrogenase deficiency. There is lack of cortisol production resulting in excess of ACTH production from the pituitary. ACTH in turn, stimulates the adrenal to produce excess androgens with virilization of female offspring. Associated aldosterone deficiency may lead to excess salt depletion. The girls are potentially fertile.

Clinical presentation.

1. Ambiguity of sex at birth.

2. Hirsutism and amenorrhea may be the presenting features around puberty in milder form.

Diagnosis at birth: enlarged clitoris, associated metabolic abnormality — salt wasting, hypotension may be present, fusion of the labia minora.

Investigations: sonographic evaluation of internal genitalia shows presence of uterus, fallopian tubes, and vagina. Sex chromatin study reveals positive Barr body. Karyotype is 46, XX.

Serum estimation: 17 hydroxy-progesterone (17 OHP) is elevated, electrolyte values are estimated to check the possibility of their depletion and producing «salt loosing syndrome» (sodium and chloride — low, potassium — raised), DHEA-S is elevated. Dexamethasone test is positive.

Management of adrenogenital syndrome: Hydrocortisone 10–20 mg/m^2 body surface area per day is given to suppress the excess ACTH secretion.

Mineralocorticoid is also given in cases with 21-hydroxylase deficiency. Cases with salt loss must be replaced carefully. Thereafter, a long-term therapy with corticosteroid is essential to suppress the adrenocortical hyperfunction. Once the neonate is stable, surgery to reduce the enlarged clitoris may be done. Reconstructive surgery includes clitoroplasty and vaginoplasty. Timing of surgery is debated. However, it is recommended to perform vaginoplasty with the onset of puberty.

POLYCYSTIC OVARIAN SYNDROME

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

This heterogenous disorder is characterized by excessive androgen production by the ovaries mainly. PCOS is a multifactorial and polygenic condition.

Diagnosis is based upon the presence of any two of the following three criteria:

1. Oligo and/or anovulation.
2. Hyperandrogenism (clinical and/or biochemical).
3. Polycystic ovaries.

Etiology. The underlying cause of PCOS is unknown. However, a genetic basis that is both multifactorial and polygenic is suspected, as there is a well-documented aggregation of the syndrome within families.

Pathology: Typically, the ovaries are enlarged. Ovarian volume is increased > 10 cm^3. Stroma is increased. The capsule is thickened and pearly white in color. Presence of multiple (> 12) follicular cysts measuring about 2–9 mm in diameter are crowded around the cortex.

Clinical features: The patient complains of increasing obesity (abdominal — 50 %), menstrual abnormalities (70 %) in the form of oligomenorrhea, amenorrhea, infertility. Presence of hirsutism and acne are the important features (70 %). Acanthosis nigricans is characterized by specific skin changes due to insulin re-

sistance. The skin is thickened and pigmented (grey brown). Commonly affected sites are nape of the neck, inner thighs, axilla.

HAIR-AN syndrome in patients with PCOS is characterized by:

- hyperandrogenism (HA);
- insulin resistance (IR);
- acanthosis nigricans (AN).

Internal examination reveals bilateral enlarged cystic ovaries which may not be revealed due to obesity.

Investigations:

1. Sonography. Ovaries are enlarged in volume (> 10 cm^3). Increased number (> 12) of peripherally arranged cysts (2–9 mm) are seen.

2. Serum values: LH level is elevated and/or the ratio LH: FSH is > 2:1. Raised level of estradiol and estrone — the estrone level is markedly elevated. SHBG (sex hormone binding globulin level is reduced. Hyperandrogenism — mainly from the ovary. Serum testosterone level is raised. Insulin Resistance (IR): raised fasting insulin levels and fasting glucose/insulin ratio < 4.5 suggests IR.

3. Laparoscopy — bilateral polycystic ovaries are characteristic of PCOS.

Pathophysiology. Exact pathophysiology of PCOS is not clearly understood. It may be discussed under the following heads:

1. Hypothalamic — pituitary compartment abnormality.
2. Androgen excess.
3. Anovulation.
4. Obesity and insulin resistance.

Hypothalamic-pituitary compartment in PCOS: increased pulse frequency of GnRH leads to increased pulse frequency of LH. Leptin (a peptide, secreted by fat cells and by the ovarian follicle), insulin resistance and hyperandrogenemia are responsible for this. Increased pulse frequency and amplitude of LH results in tonically elevated level of LH. FSH level is not increased. This is mainly due to the negative feedback effect of chronically elevated estrogen and the follicular inhibin. Increased free estradiol due to reduced sex hormone binding globulin (SHBG) bears positive feedback relationship to LH.

Androgen excess. Abnormal regulation of the androgen forming enzyme

(P450) is thought to be the main cause for excess production of androgens from the ovaries and adrenals. Ovary produces excess androgens due to stimulation of theca cells by high LH, P450 enzyme hyperfunction, defective aromatization of androgens to estrogen, stimulation of theca cells by IGF-1 (insulin growth factor-1).

Anovulation: Because of low FSH level, follicular growth is arrested at different phases of maturation (2–10 mm diameter). Due to elevated LH, there is hypertrophy of theca cells and more androgens are produced either from theca cells or stroma. There is huge number of atretic follicles that contribute to increased ovarian stroma (hyperthecosis). LH level is tonically elevated without any surge. LH surge is essential for ovulation to occur.

Obesity and insulin resistance. Apart from excess production of androgens, obesity is also associated with reduced SHBG. It also induces insulin resistance and hyperinsulinemia which in turn increases the gonadal androgen production. Etiology of insulin resistance is unknown. Mutations of the insulin receptor gene in the peripheral target tissues and reduced tyrosine autophosphorylation of the insulin receptor, is currently thought to be an important cause. Increased central body fat leads to android obesity.

Management of PCOS needs individualization of the patient. It depends on her presenting symptoms, like menstrual disorder, infertility, obesity, hirsutism or combined symptoms.

Weight reduction in obese patients is the first line of treatment. Body mass index (BMI) < 25 improves menstrual disorders, infertility, impaired glucose intolerance (insulin resistance), hyperandrogenemia (hirsutism, acne) and obesity.

Fertility not desired: management of hyperandrogenemia. Combined oral contraceptive pills are effective. Progestin suppresses LH and estrogen improves SHBG, reducing free testosterone level. Newer progestins (desogestrel) are best suited. Hirsutism is due to anovulation, high androgen

and insulin levels, decreased hepatic SHBG production. Correction of metabolic syndrome improves it. Antiandrogens (cyproterone acetate, spironolactone, flutamide) may be used.

Metabolic syndrome: Hyperinsulinemia (insulin resistance) causes hyperandrogenemia. Insulin resistance is associated with diabetes mellitus, central obesity, dyslipidemia and hypertension. Metformin, increases insulin sensitivity, decreases weight and reduces cholesterol, blood pressure. 500 mg thrice daily is found to correct the biochemical abnormalities.

Patient desires pregnancy. Chronic anovulation is the common cause of infertility. Improvement of metabolic syndrome is essential. Ovulation induction is usually achieved by clomiphene citrate following correction of other biochemical abnormalities.

Surgery. Laparoscopic ovarian drilling (LOD) is done for cases found resistant to medical therapy. It has replaced the conventional wedge resection of the ovaries. Pregnancy rates following ovarian diathermy are higher.

HYPERPROLACTINEMIA

Hyperprolactinemia is one of the most frequently diagnosed endocrine disorders in women. It is defined as the consistent presence of an abnormally high level of prolactin in the blood when physiological causes have been excluded. Prolactin is secreted from lactotrophs of the anterior pituitary, and its main physiological role is to promote milk secretion. It is normal for serum prolactin levels to rise during pregnancy and breastfeeding. The most significant regulatory substance for prolactin secretion is dopamine, which is tonically secreted from

the hypothalamus. Anything that interferes with dopamine synthesis, its transport to the pituitary gland, or the binding and activation of the dopamine receptor on the lactotroph can result in hyperprolactinemia.

Hyperprolactinemia and amenorrhea. Prolactin inhibits GnRH pulse secretion, gonadotropin levels are suppressed. Hyperprolactinemia inhibits ovarian steroidogenesis, which lead to anovulation and hypogonodotropic hypagonadism.

There are a variety of mechanisms by which prolactin may be present in excess, and these can generally be broken down into ***physiologic***, ***pathologic,*** and ***medication-induced*** causes.

Causes of hyperprolactinemia:

1. Physiological (stress and exercise, pregnancy, sleep, idiopathic).

2. Hypothalamus and pituitary (tuberculosis, hypothyroidism, multiple endocrine disorder, pituitary adenomas).

3. Drugs (phenothiazines, metoclopramide, methyldopa, reserpine, antidepressants, estrogens).

Pituitary adenoma (prolactinoma). Hyperprolactinemia is most frequently caused by a prolactinoma, which is the most common type of benign pituitary adenoma. Prolactinomas < 10 mm are ***microprolactinomas***, and those ≥ 10 mm are *macroprolactinomas*.

Diagnosis of pituitary adenomas. Prolactin level is more than 100 ng/mL is often associated with prolactinoma. Most of the adenomas are microadenoma. Microadenomas rarely progress to macroadenomas. Computerized tomography (CT) is helpful for macroadenomas. Magnetic resonance imaging (MRI) with better resolution is superior to CT. MRI has no radiation risk.

Treatment. Medical: Bromocriptine — a dopamine agoinst is the drug first choice. Common side effects are: giddiness, nausea, vomiting, headache, constipation and orthostatic hypotension. Cabergoline is a selective dopamine agonist. It has less side effects, greater potency and longer duration of action. It is given 0.25 mg or 0.5 mg once or twice weekly. Prolactin levels usually decrease within 2–3 weeks of treatment. Menses, ovulation and fertility return when prolactin level returns to normal.

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

SHEEHAN'S SYNDROME

Sheehan's syndrome — there is partial or complete destruction of the pituitary by ischemia caused by venous thrombosis following severe postpartum hemorrhage and shock.

The principal hormones affected are growth hormone, gonadotropins, prolactin.

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

The common manifestations are failing lactation, loss of pubic and axillary hair, hypotension, secondary amenorrhea and atrophy of the breasts and genitalia.

Diagnosis. Gonadotropin level is low, so also T3, T4 and cortisol. The hormones affected in order of frequency are, growth hormone (GH), prolactin, gonadotropins (FSH and LH), TSH and ACTH. The syndrome may develop slowly over 8–10 years time.

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

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Учебно-методическое пособие на английском языке для студентов 5 и 6 курсов факультета по подготовке специалистов для зарубежных стран медицинских вузов

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