Diabetes mellitus. 2013;(3):103–108

Менопаузальный синдром у женщин с сахарным диабетом

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У женщин с нарушениями углеводного обмена выявляется иная структура проявлений климактерического синдрома, имеющая уникальные особенности. У пациенток с сахарным диабетом 1 типа менопауза наступает раньше – в 46–48 лет. Сахарный диабет не является противопоказанием для назначения заместительной гормональной терапии (ЗГТ). Выбор режима ЗГТ должен определяться индивидуально в каждом конкретном случае.
***Ключевые слова**: сахарный диабет; заместительная гормональная терапия; перименопауза; постменопауза*

Climacteric syndrome in women with diabetes mellitus

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Climacteric syndrome in women with glycemic disorders is known to have several unique features, including earlier onset in women with type 1 diabetes mellitus (usually at the age of 46–48 years). However, diabetes mellitus is not a contraindication for hormone replacement therapy (HRT), though the appropriate age for its introduction should be determined on a case-by-case basis.
***Keywords:** diabetes mellitus; hormone replacement therapy; perimenopause; post menopause*

DOI: http://dx.doi.org/10.14341/2072-0351-824

Currently, the number of patients with diabetes mellitus (DM) in the world is more than 371 million people, 50% of which do not know about their disease [1]. In Russia, as in all countries high growing rates of diabetes remain, mainly due to patients with type 2 diabetes mellitus (T2DM). According to the State register of patients with DM in the last 10 years the number of patients with T2DM increased in 2 times and reached more than 3 million people (January 2009). The results of epidemiological studies, conducted in Endocrinology Research Center from 2002 to 2009, showed that about 6 million russians still have type 2 diabetes but do not know it and therefore do not receive treatment [2]. It is noted that women over 45 years old suffer from DM 2 times more often than men [3]. Thus, the DM can be called an epidemic of 21st century.

The prevalence of overweight and obesity in the world is steadily increasing, according to the World Health Organization (WHO) in 2008 more than 1,4 billion adults aged twenty years and older are overweight, of which more than 200 million are men and about 300 million are obese. The WHO's experts predict that by 2025 the number of obese will increase almost 2-times and high growth rates and the prevalence of the disease allow to call it a new "non-infectious epidemic" [4]. According to the survey of a national sample of adults in Russia prevalence of overweight and obesity ranges from 45 to 56% in men and from 56 to 62% in women [5].

Menopause – is a natural biological process of transition from the reproductive period of a woman's life to old age, which is characterized by a gradual ovarian failure, decreased estrogen levels, termination of menstrual and reproductive function. The average age of menopause for women in Europe and Russia is 50-51 years old. Thus estrogen deficiency in women exists within one third of their lives [6]. Menopausal syndrome (MS) develops in estrogen deficiency, accompanied by a complex of pathological symptoms that occur depending on phase and duration of this period. The earliest symptoms of MS in patients without endocrinopathy are autonomic disturbances (hot flashes, sweating, instable blood pressure, palpitation, tachycardia, extrasystole, dizziness) and psychological disorders (mood instability, depression, irritability, fatigue, sleep disturbance), in 25-30% of patients these complaints remain more than 5 years [7].

According to the retrospective analysis, menopause in women with type 1 diabetes mellitus (T1DM) occurs earlier compared to women from the general population. Thus, J. S. Dorman et al. found that menopause in women with T1DM occurred at an earlier age than in women without T1DM (41.6 and 48.0 years, respectively) [8]. In a study conducted in Finland a decade later, age of menopause in women with T1DM did not significantly differ from that in the general population. Significant factors independently associated with an earlier onset of menopause were microvascular complications of underlying disease, such as terminal stage of diabetic nephropathy and proliferative retinopathy [9]. N. Soto et al. found that Anti-Mullerian hormone level,

accurately reflecting the follicular reserve, begins to decline at age 33 in healthy women and in patients with diabetes, but in diabetic women after the age 33 its level is significantly lower compared to women the same age without carbohydrate metabolism disorders [10]. It is expected that due to the development of premature ovarian failure in women with T1DM great value is given to the direct toxic effect of persistent hyperglycemia on the viability of the oocyte and autoimmune reactions (formation of autoantibodies to the ovaries and adrenal glands). After unilateral adnexectomy in women with T1DM the risk of early menopause increases 10 times compared to women with saved ovaries [8, 10]. As for T2DM, it was shown that menopause occurs earlier in women suffering from this disease in comparison with healthy (46 and 48 years old, respectively) [11]. The same time, in another study T2DM was not associated with a change in the age of menopause [12]. Menopausal vasomotor symptoms in women with diabetes are mild and tend to overlap psychological disorders [13]. It should be noted that 90% of women with diabetes have urogenital complaints – dryness, itching and burning in the vagina, dyspareunia, urinary incontinence. This is due to the fact that the decrease in estrogen level after menopause leads to the progressive atrophic processes in the mucosa of urethra, vagina, bladder, pelvic ligaments and the periurethral muscles. In addition, a long glycosuria and development of neuropathy with lesion of the bladder play an important role in the development of urinary tract infection in women with DM on the background of estrogen deficiency [14].

Breakthrough on a problem of increasing the age of woman's life and improve the quality of life was the use of hormone replacement therapy (HRT) [15]. In the period of 1980-1990's, with the rising interest in use of HRT in healthy women, a group of diabetic patients remained in the shadows, which was associated with the presence of potential contraindications to the use of HRT. In the period of 1990 – 2000's improved compensation of DM and prevention of cardiovascular events in these patients could be obtained through HRT on the basis of experimental data.

Results of researches PEPI, HERS, WHI, MWS and others, published in 1999 – 2002, have led to the refinement of indications and basic principles of hormone replacement therapy (estrogen only therapy in women with uterus removed, minimum effective dose, individualization of type and duration of therapy and assessment benefit/risk ratio). The modern concept of HRT does not mean a continuous therapy in all postmenopausal women and is appointed by indications. HRT is not assigned only for the prevention of cardiovascular disease or dementia in the absence of post-menopausal symptoms. Optimal terms of HRT are premenopausal and early postmenopausal period (within the first 5 years after the last menstrual period), when the frequency and severity of complaints are maximal and it is possible to get the preventive effects of HRT. "The beginning of hormonal therapy in premenopausal women provides for prevention of complications such as fractures and heart disease," so-called "window of opportunities" [6].

In 2012, on the initiative of the International Menopause Society with the participation of leading national societies for menopause international consensus on menopausal hormone therapy has been developed. This document was published in 2013, it contains the key points on which consensus was reached:

1. Menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause.
2. MHT is effective and appropriate for the prevention of osteoporosis-related fractures in at-risk women before age 60 years or within 10 years after menopause.
3. Randomized clinical trials and observational data as well as meta-analyses provide evidence that standard-dose estrogen-alone MHT may decrease coronary heart disease and all-cause mortality in women younger than 60 years of age and within 10 years of menopause. Data on estrogen plus progestogen MHT in this population show a similar trend for mortality but in most randomized clinical trials no significant increase or decrease in coronary heart disease has been found.
4. Local low-dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse.
5. Estrogen as a single systemic agent is appropriate in women after hysterectomy but additional progestogen is required in the presence of a uterus.
6. The option of MHT is an individual decision in terms of quality of life and health priorities as well as personal risk factors such as age, time since menopause and the risk of venous thromboembolism, stroke, ischemic heart disease and breast cancer.
7. The risk of venous thromboembolism and ischemic stroke increases with oral MHT but the absolute risk is rare below age 60 years. Observational studies point to a lower risk with transdermal therapy.
8. The risk of breast cancer in women over 50 years associated with MHT is a complex issue. The increased risk of breast cancer is primarily associated with the addition of a progestogen to estrogen therapy and related to the duration of use. The risk of breast cancer attributable to MHT is small and the risk decreases after treatment is stopped.
9. The dose and duration of MHT should be consistent with treatment goals and safety issues and should be individualized.
10. In women with premature ovarian insufficiency, systemic MHT is recommended at least until the average age of the natural menopause.

11. The use of custom-compounded bioidentical hormone therapy is not recommended.
12. Current safety data do not support the use of MHT in breast cancer survivors.

In a large meta-analysis of 107 randomized controlled trials (RCTs) S.R. Salpeter et al. have shown that HRT reduces the risk of DM by 30% compared with placebo or no treatment. In addition, women with DM and no HRT were observed less expressed abdominal obesity and waist circumference, as well as a more favorable lipid profile [17].

According to a meta-analysis of S. R. Salpeter et al. in women with DM treated with HRT lower concentration of glucose and fasting insulin were observed, and insulin resistance was less expressed in comparison with patients receiving placebo or without treatment [17]. Nevertheless, the authors of systematic Cochrane review published in 2013, concluded that currently the amount of data on the use of HRT in women with T1DM is not enough. These authors reviewed the results of only one RCT, which included women with T1DM and T2DM. In this study lipid profile, glycemia, blood pressure and BMI were not significantly different in groups of women taking HRT and placebo [18]. According to Kaiser Permanente Medical Care Program of Northern California women with T2DM taking HRT have lower levels of glycated hemoglobin than women of similar age group without carbohydrate disorders (regardless of age, ethnicity, body weight, duration of DM) [19]. The beneficial effect of estrogen at reducing level of glycated hemoglobin is probably due to the improvement in insulin sensitivity and suppression of gluconeogenesis in the liver [20].

At present, experimental and clinical data show renoprotective effect of estradiol. In the culture of mesangial cells estradiol inhibits apoptosis, increases the expression of metalloproteinases and reduces collagen type I and IV. B. Szekacs et al. have shown that taking a combination of estradiol and norgestrel led to a decrease of proteinuria and improvement of creatinine clearance in women with DM and hypertension [21].

Currently, DM is not a contraindication to the use of HRT, and general guidelines on the use of hormone replacement therapy in this group of women do not differ from those of their healthy peers. Particular attention is given to patients with an increased risk of coronary heart disease, which is the main cause of mortality in postmenopausal women. In women with DM the risk of coronary heart disease is increased and associated with dyslipidemia, obesity, hypertension and increased inflammation. B.V. Howard, et al. found that HRT in women with impaired glucose tolerance leads to the progression of atherosclerosis, which is accompanied by an increase in the level of C-reactive protein [22]. According to Kaiser Permanente Medical Care Program of Northern California use of estrogen-progestogen HRT resulted in an increased risk of heart attack in women recently survived this disease and reduced risk in patients who did not have it in the recent past [19]. Several studies have shown that HRT in women with DM does not provide a protective effect on the cardiovascular system [23]. S. Lamon-Fava et al. have shown that coronary artery disease with HRT progresses significantly greater in women with DM compared to patients without carbohydrate disorders [24].

Components of the "diabetic" (metabolic) dyslipidemia, evolving under the influence of insulin resistance are the increase in triglycerides (TG), a decrease in HDL cholesterol and overproduction of LDL cholesterol. In a study K.E. Friday et al. had a significant decrease in postprandial triglyceride levels in women with DM on HRT compared with placebo [25]. S. Lamon-Fava found no significant increase in triglycerides with HRT in patients with DM, which, however, did not differ significantly from that in women without carbohydrate disorders. In addition these authors have shown that in women with DM increased concentration of HDL subpopulations with HRT was significantly less expressed in comparison with healthy peers[24].

DM is accompanied by adverse disorders in the hemostasis. This is shown in increase of adhesion and aggregation of platelets, increase of fibrinogen, factor V, VII and VIII and plasminogen activator inhibitor-1, in the imbalance of thrombin-antithrombin complex, which contributes to thrombogenesis. However, the currently available limited data on the effect of HRT on coagulation in women with T2DM showed an improvement in fibrinolysis indicators on the background of its use[26].

Selection of components for HRT in women with DM should be individualized, with a view to leveling the adverse biological effects of sex steroids on the blood lipid profile, coagulation system / fibrinolysis and achieving positive results. Metabolically neutral progestogen should be used with parenteral route of administration.

Bioavailable estrogen has a cardioprotective effect (in carbohydrate and lipid metabolism, hemostatic system). The effect performed by reducing the risk factors for cardiovascular disease, and improving the vascular endothelial function (by activation of nitric oxide synthesis and prostacyclin, helping to reduce vascular resistance). Thus physiological HRT is possible only with parenteral forms [27].

Ability to absorb sex steroids varies at every patient and depends on the distribution of estrogen receptors and their affinity for exogenous estradiol involving the vascular endothelium. According to current data, estrogens may have a direct effect on the accumulation of glycogen in the liver, decrease glucagon secretion and increase the sensitivity of muscles to absorb glucose, leveling manifestations of insulin resistance. Adverse changes in carbohydrate metabolism does not occur, and also there is no increase in body weight when estrogen is used with transdermal route of administration

(in the absence of first-pass liver) [23]. Also in contrast to oral route of administration, transdermal therapeutic dose of estrogen does not lead to increased levels of estrone, triglycerides, angiotensin and reduced levels of antithrombin III [28].

It is important that effect of HRT on carbohydrate and lipid metabolism depends not only on the dose of estrogen and chemical formula and the route of administration, but also on the presence or absence of progestogen component.

Currently, in the presence of a uterus administration of progestogen for 10–14 days is compulsory in order to prevent the development of endometrial hyperplasia in peri-and postmenopausal women. The optimal regime of HRT for postmenopausal women is a continuous administration of progestogens, which leads to atrophy of the endometrium and the absence of withdrawal bleeding. In this case, duration of administration of progestogens is more important for reducing the frequency of endometrial hyperplasia than their daily dose. Low-dose and progestogen cyclic reception can reduce their negative impact on lipid levels [29].

It is now considered that progesterone binds to cytolytic receptors of β-cells in the pancreas. Progesterone and progestins may promote the development of insulin resistance in peripheral tissues by reducing glucose uptake in skeletal muscle and lipids [30]. Micronized natural progesterone does not interact with estrogen and can be used orally or parenterally. In postmenopausal women micronized progesterone in optimal doses does not reduce the level of HDL- cholesterol, it has no effect on the metabolism of glucose and does not eliminate the beneficial effects of estrogen on the endothelium. It has many positive effects: its anti-aldosterone effect, antiandrogenic effect by blocking 5-α-reductase and interaction with receptors of testosterone in the endometrium, a neuroprotective effect, beneficial effects on mood and sleep [13, 30].

Medroxyprogesterone acetate (MPA) and levonorgestrel in oral form have a negative effect on carbohydrate metabolism -they lead to the poor glucose tolerance [31]. Norethisterone acetate has a neutral effect on carbohydrate metabolism. Biological effects of these progestogens are significantly different from micronized progesterone. This is especially important when comparing MPA and micronized progesterone. MPA reduces the beneficial effect of HRT on blood lipid profile and impairs peripheral insulin function [29]. In 2005 Sites C. K. showed a reversible appearance of insulin resistance for 2-years period of HRT in 26 women treated with conjugated estrogen and MPA [32].

Dydrogesterone (retroprogesterone) in chemical structure and pharmacological action is analogous to natural progesterone, but unlike it has a predictable bioavailability after oral administration. Dydrogesterone has only progestogen activity and is deprived of anabolic or androgenic effects, as well as glucocorticoid effects. Consequently, dydrogesterone does not eliminate the protective effect of estrogens on the cardiovascular system, which has particular advantages in the administration of this drug in women with DM and obesity without hypertriglyceridemia. Dydrogesterone, designated in cyclic mode 20 mg daily did not affect the sensitivity to insulin, and 10 mg daily may reduce the concentration of insulin [33, 34].

Fourth generation of progestogens is drospirenone, a special progestin with progesterone, anti-aldosterone and antiandrogenic effect, a positive effect on blood lipid profile, it improves blood pressure and has no effect on carbohydrate metabolism [35, 36]. Several studies have shown that 2 mg of drospirenone daily is minimally effective dose in reducing blood pressure [37]. It should be emphasized that drospirenone is not a drug for treatment of hypertension, and in women with this pathology it should be administered with caution in combination with antihypertensive drugs. O.R. Grigoryan et al. also showed that drospirenone is an optimal drug providing additional therapeutic benefit in post-menopausal women with hypertension and DM [38].

Thus, it is preferable to use the following progestins in medication for HRT in women with DM: micronized progesterone, retroprogesterone-dydrogesterone and drospirenone and follow the provisions:

1. The lowest dose of estrogen is needed to be balanced by proportional dose of progestogen.
2. It is necessary to consider all aspects in preserving woman's health, choosing the dose of estrogen.
3. Choice of progestogen is very important for women with obesity and / or impaired glucose metabolism. Preference is given to neutral progestogens.
4. The only way to achieve these aims in women with hypertriglyceridemia is administration of 17β-estradiol in the form of a gel and micronized progesterone (in the presence of a uterus).
5. Levels of estradiol and follicle-stimulating hormone should be regularly assessed to control the acceptability and variability of absorption and binding of sex steroids.

These guidelines apply especially to patients with obesity / or hypertriglyceridemia. The duration of treatment and the dose of estrogen and progestogen components should be selected individually. HRT is not conducted in patients with a BMI greater than 40 kg/m^2 as long as the body weight will be reduced by 10% from the initial. Selection of HRT should be determined individually in each case.

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