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The Impact of Menopausal Hormone Therapy on Liver and Biliary Tract Health

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Aim: to provide summarized data on the relationship between menopausal hormone therapy (MHT) and liver health.
Key points. A decrease in estrogen production during the menopausal transition and a deficiency of estrogen and progesterone during postmenopause significantly affect lipid and carbohydrate metabolism and can lead to impaired liver function. With age, the risk of developing metabolic-associated fatty liver disease (MAFLD) in women increases significantly, due to a combination of hormonal changes, a higher incidence of metabolic disorders, and age-related factors. In turn, MAFLD is associated with an increased risk of cardiovascular disease, diabetes mellitus and metabolic disorders. In the absence of well-timed hormonal support, postmenopausal women are at high risk of developing serious complications, therefore, it is extremely important to select MHT with a favorable efficacy and safety profile. The approach to prescribing MHT should take into account the patient's medical history, individual characteristics, as well as the mode of drug administration, considering the minimum effective dose.
Conclusion. Oral combination MHT provides positive metabolic effects through the first-pass metabolism but is not associated with additional health risks.
Keywords: estrogen deficiency, metabolic-associated fatty liver disease, cholelithiasis, lipid profile, menopausal hormone therapy
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Влияние менопаузальной гормональной терапии на состояние печени и желчевыводящих путей

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Цель: представить обобщенные данные по связи менопаузальной гормональной терапии (МГТ) с состоянием печени.
Основные положения. Снижение продукции эстрогенов в период менопаузального перехода и дефицит эстрогенов и прогестерона во время постменопаузы существенно влияют на липидный и углеводный обмен и могут приводить к нарушениям функционирования печени. С возрастом риск развития неалкогольной, а точнее метаболически ассоциированной жировой болезни печени (МАЖБП) у женщин значительно возрастает, что вызвано сочетанием гормональных изменений, более высокой частотой развития инсулинорезистентности, нарушений обмена глюкозы и липидов, увеличения массы тела. В свою очередь, МАЖБП ассоциируется с повышенным риском сердечно-сосудистых заболеваний, сахарного диабета и прогрессирования метаболического синдрома. В отсутствие своевременной гормональной поддержки женщины в постменопаузе подвержены бóльшим рискам развития серьезных осложнений, в связи с чем крайне важно подобрать МГТ с благоприятным профилем эффективности и безопасности. Подход к назначению МГТ должен учитывать анамнез, индивидуальные характеристики пациентки, а также форму приема препарата с учетом минимально эффективной дозы.
Заключение. Пероральная комбинированная МГТ за счет эффекта первичного прохождения через печень обеспечивает положительные метаболические эффекты и при этом не ассоциирована с дополнительными рисками для здоровья.

Ключевые слова: дефицит эстрогенов, метаболически ассоциированная жировая болезнь печени, желчнокаменная болезнь, липидный профиль, менопаузальная гормональная терапия
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Introduction

Chronic liver and biliary tract diseases are a major global health problem. Liver diseases cause two million deaths worldwide each year and are responsible for one in every 25 deaths; approximately two-thirds of all liver-related deaths are associated with the male gender. The risk of death from liver disease increases with age [1, 2]. A systematic review and meta-analysis of 115 studies involving 32,610,568 people showed that cholelithiasis develops in 6.1 % of the world population (95 % confidence interval (95 % CI): 5.6–6.5). The incidence of cholelithiasis is higher in women (7.6 %) than in men (5.4 %) and increases with age [3]. Epidemiological data in the Russian Federation also indicate a high incidence and social significance of liver and gallbladder diseases [4, 5]. With increasing age, the burden of liver and biliary tract diseases increases regardless of gender.

Problems associated with liver and cholelithiasis in women have certain characteristics: not only age, but also hormonal factors, such as estrogen deficiency, affect the induction and progression of the pathological process. It is noted that this interaction of factors is especially significant in the postmenopausal period.

It is estimated that by 2025, approximately 1.1 billion women worldwide will be postmenopausal [6]. The average age of natural menopause in the Russian Federation is 48–51 years [7], with approximately 1,000,000 women in Russia entering this period annually. It is certainly important that the course and management of chronic liver disease in women be understood in the unique context of their mediation by the onset of menopause and the estrogen deficiency that develops during this period.

The effect of estrogens on liver function

Normally, estrogens have a positive effect on liver function and prevent the development of its dysfunction [8, 9]. Estrogens are involved in the regulation of lipid and carbohydrate metabolism. Estrogens lead to suppression of gluconeogenesis, decrease in insulin resistance, limitation of free fatty acids (FFA) consumption and inhibition of de novo lipogenesis in the liver. Increased mitochondrial activity in hepatocytes under the estrogen effect promotes oxidation and export of free fatty acids, preventing the accumulation of lipids and the development of lipotoxicity, as well as proinflammatory free radicals accumulation [8–10]. Estrogens may also exert anti-inflammatory effects by regulating Kupffer cell activity and enhancing phagocytosis. It is suggested that estrogens also inhibit the activation of stellate cells and their transformation into myofibroblasts, thereby preventing the progression of fibrosis [8, 9].

Preclinical studies confirm the hepatoprotective effect of estrogens. 17β-estradiol has been shown to enhance hepatocyte proliferation [11, 12], stimulate mitochondrial biogenesis and enhance mitochondrial function, promoting reduced oxidative stress and less lipid accumulation in the liver [13]. Hepatocellular carcinoma is more common in men than in women, which may also be due to the hepatoprotective effect of estrogens. 17β-estradiol has been shown to inhibit the JAK1-STAT6 signaling pathway, thereby inhibiting tumor growth by suppressing alternative activation of macrophages [14]. There is evidence that 17β-estradiol administration leads to a decrease in the synthesis of interleukin-6 (IL-6), one of the main proinflammatory cytokines associated with tumor growth [15]. In preclinical studies, lower estrogen expression was observed in metabolically active tissues in male mice compared to female mice, which contributed to the development of obesity, impaired glucose tolerance, hepatic steatosis, inflammation in adipose tissue and liver [16].

Metabolic-associated fatty liver disease in women over 45 years old

Non-alcoholic fatty liver disease (NAFLD) is a common chronic pathology associated with abnormal accumulation of lipids, mainly in the form of triglycerides (TGs), in the liver lobules. The severity of NAFLD varies from simple steatosis with no inflammatory process to nonalcoholic steatohepatitis, which is characterized by inflammation, ballooning degeneration of hepatocytes, tissue necrosis and rapid progression of fibrosis [17]. The presence of NAFLD is associated with an

increased risk of developing more serious pathological conditions, such as decompensated liver cirrhosis and hepatocellular carcinoma [17–19].

The prevalence of NAFLD is increasing worldwide: according to recent estimates, the disease occurs in approximately 30 % of cases in the global population [20]. It is expected that NAFLD may affect more than half of the adult population in the coming decades, in parallel with the increase in the incidence of type 2 diabetes mellitus (T2DM) and obesity [21].

It has been established that NAFLD is bidirectionally interconnected with the presence of metabolic disorders that are associated with increased accumulation of lipids in the liver [22, 23]. The incidence of NAFLD in overweight or obese patients is about 70 % [24], and in patients with T2DM, it is about 50 % [25]. Given the undeniable role of metabolic disorders in the pathogenesis of the disease, an international expert group proposed a new term in 2020 — metabolic dysfunction-associated fatty liver disease (MAFLD) [22, 23]. However, Russian experts recommend retaining the established term NAFLD in accordance with the internationally accepted disease classification, while incorporating the updated diagnostic criteria [17].

In the pathogenesis of NAFLD there are several main pathogenetic mechanisms — the so-called shocks or jolts. In obesity, the role of the first shock is the initial accumulation of fatty acids and TG in the hepatocyte. The liver becomes the site of accumulation TG, which are synthesized from dietary fatty acids or carbohydrates — glucose and fructose [28]. In insulin resistance (IR) and diabetes, the source of fatty acids is TG lipolysis from adipose tissue, and in the absence of obesity without dietary overload of fatty acids, the resulting neutral fat accumulates in subcutaneous brown adipose tissue as a source of reserve energy [29]. Further deposition of fat (in liver, pancreas, myocardium and even skeletal muscles) occurs after overloading of adipose tissue with circulating TGs in the blood. As a result, the liver becomes a place of TG accumulation, and brown adipose tissue becomes a reservoir of energy substrates [30]. Such accumulation of TGs (both in adipose tissue, as well as ectopic) is accompanied by damage to a part of hypertrophied adipocytes or hepatocytes, to them subsequently migrate activated immunocytes (macrophages), which secrete cytokines and activate immune reactions of delayed type — chronic systemic inflammation develops [31].

Altered adipose tissue secretes lipokines, of which adiponectin and leptin are the most important for the pathogenesis of NAFLD [32]. Overloaded fatty tissues reduce or lose sensitivity to the regulatory effect of insulin and other regulatory hormones and mediators, and IR develops. In effect, the liver takes over the functions of white adipose tissue — synthesizes proinflammatory and prohyperglycemic lipokines, which deepens IR [32, 33].

The second stage of NAFLD progression is the development of a chronic inflammatory process. Against the background of insulin resistance, the normal regulation of lipolysis in adipose tissue is disrupted, which, in turn, leads to an increase in the level of FFA in the blood. This process is also associated with impaired mitochondrial function and a decrease in their ability to oxidize FFA. High concentrations of FFA contribute to lipid peroxidation reactions with the release of toxic free radicals, as well as oxidative stress. This process is accompanied by hyperactivation of immune cells and Kupffer cells with increased production of pro-inflammatory cytokines, which contributes to further damage to the cellular structures of the liver. Against the background of chronic inflammation, fibrosis is induced, leading to the progression of loss of liver function [32–34].

NAFLD is characterized by gender differences, which is associated with the hepatoprotective effect of estrogens. The prevalence of NAFLD among the adult population of reproductive age is higher in men than in women [35]. However, unlike in men, the incidence of NAFLD begins to increase in women over 45 years of age due to the onset of menopause, peaking at 60–69 years of age and then declining in old age (≥70 years) [36, 37]. The high prevalence of NAFLD in women over 45 years of age is associated with changes in hormonal levels, as well as an increased predisposition to metabolic disorders. After menopause, the ovaries stop secreting estrogen, causing the hormone levels in the blood to decrease. Since estrogens play an important role in the regulation of lipid and glucose metabolism in the liver and adipose tissue, a decrease in their levels during menopause increases the likelihood of developing both NAFLD and T2DM, central obesity and dyslipidemia, risk factors of NAFLD progression [38, 39].

In addition to reduced estrogen secretion, postmenopausal women experience an increased risk of metabolic disorders: insulin resistance, glucose and lipid metabolism disorders, and weight gain. Obesity can be considered as one of the most significant disorders associated with menopause, since it is also associated with an increased risk of NAFLD development. In obese patients, an increased secretion of free fatty acids by adipocytes is observed on the background of more active lipolysis. Obesity is also associated with the development of insulin resistance, which reduces the

synthesis of glycogen in myocytes. At the same time, carbohydrate levels increase, and de novo lipogenesis is activated in the liver, leading to excessive accumulation of lipids in the liver. Excess lipids and carbohydrates induce oxidative stress, mitochondrial disorders and activation of inflammatory signaling pathways. All these pathophysiological mechanisms are interconnected and create a "vicious circle" that contributes to the progression of NAFLD in obese patients [38–40].

Liver diseases can lead to metabolic disorders such as insulin resistance and dyslipidemia, which in turn increase the risk of developing atherosclerosis and other cardiovascular diseases. Population studies demonstrate that NAFLD is associated with an increased risk of myocardial infarction, stroke, and heart failure [17, 41–44]. NAFLD requires well-timed detection and adequate pharmaceutical correction to reduce the risk of life-threatening complications among women over 45 years of age during peri- and postmenopause.

Cholelithiasis

Cholelithiasis is associated with risk factors such as female gender, age and genetic characteristics. Obesity, metabolic syndrome, liver disease, and a sedentary lifestyle also facilitate gallstones formation [45]. The prevalence of cholelithiasis has remained consistently high over the past decades with the presence of gallstones more often observed in women (7.6 %) [6].

Gender differences in the incidence of cholelithiasis begin at puberty and persist throughout the reproductive period. Pregnancy and childbirth, as well as hormone therapy for contraception or during menopause, are associated with an increased risk of cholelithiasis [46]. It is believed that estrogen stimulates the secretion of cholesterol in the liver, which leads to saturation of bile with cholesterol and its accumulation in the gallbladder. Also, high estrogen levels significantly increase the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which promotes the synthesis of cholesterol de novo and its subsequent excess secretion into the bile [47].

Clinical studies have shown that the likelihood of developing cholelithiasis was higher in women who received higher doses of estrogen as hormone therapy, compared with women who received stable low doses of hormones [46, 47].

Menopause and liver. Are there any options for menopausal hormone therapy?

As estrogen and progesterone levels decline during menopause, women may experience a number of unpleasant symptoms that can be corrected with menopausal hormone therapy (MHT). In addition to reducing the severity of menopausal symptoms and improving the patients' quality of life, MHT is also necessary to prevent long-term complications associated with hormone deficiency, such as osteoporosis and cardiovascular diseases risk [7].

It is important to highlight the ability of early MHT initiation. Since reducing the risks of atherosclerosis, cardiovascular diseases, metabolic syndrome, and T2DM, MHT improves the quality of life of patients over 45 years of age. Choosing a rational MHT requires an individual approach. A personalized approach to MHT should take into account the risk factors for cardiovascular diseases, breast cancer and postmenopausal osteoporosis, the presence of comorbid conditions, the stage of reproductive aging according to the STRAW+10, as well as the individual wishes of the patient. When selecting the optimal MHT, the minimum effective dose is determined, as well as the most appropriate dosage form. Currently, progestogen and estrogen preparations are available for monotherapy or combination therapy, which can be administered oral, transdermal, or vaginal [7].

Numerous clinical studies demonstrate the benefits of MHT in normalizing carbohydrate and lipid metabolism, but the treatment efficacy varies significantly depending on the product form. All active ingredients of MHT products are metabolized in the liver, regardless of the dosage form. However, unlike transdermal MHT, when administered orally, estradiol undergoes a "first pass" through the liver before entering the systemic circulation, which may contribute to a greater metabolic effect of therapy.

A systematic review of 12 studies comparing the effects of oral and transdermal MHT on lipid metabolism found that replacement therapy reduced low-density lipoprotein (LDL) levels regardless of the route of administration. Oral MHT has been shown to increase high-density lipoprotein (HDL) and TG levels. High HDL levels are associated with a reduced risk of atherosclerosis and cardiovascular disease. In contrast, transdermal MHT has no significant effect on HDL levels. In addition, some studies did not find a statistically significant effect of transdermal therapy on reducing the levels of LDLs, the most atherogenic type of lipoprotein. Most studies of transdermal MHT have shown significant reductions in TG levels [48].

Oral estrogen administration has a positive effect on the lipid profile in women after ovarian failure due to menopause. Oral estrogen effect results in significantly lower LDL-cholesterol and lipoprotein (a) (Lp(a)) levels, but higher HDL-cholesterol and TG levels. Transdermal

17β-estradiol MHT is associated with a neutral effect on TG levels, albeit a less beneficial effect on LDL-C, HDL-C, or Lp(a) levels. Differences may be mediated by the drug's mechanism of action. When taken orally, estrogens are metabolized in the liver before entering the systemic circulation, which provides a "first pass" effect that enhances the drug effect. With transdermal MHT, estrogens enter the systemic circulation directly through the skin, without affecting lipid metabolism in the liver. There is also evidence of a positive effect of the combination of estrogen and progestogen on the lipid profile, especially with respect to TGs. However, monotherapy with medroxyprogesterone acetate, levonorgestrel, desogestrel, and norgestrel appears to be associated with an adverse effect on the lipid profile, and especially on HDL-cholesterol levels [49].

The importance of MHT in the correction of metabolic-associated liver dysfunctions is discussed. The postmenopausal period in women is characterized by pronounced changes in metabolism, including the development of dyslipidemia and insulin resistance. These conditions are associated with an increased influx of FFAs into the liver, which in turn leads to steatosis and NAFLD progression. In addition, estrogen deficiency in the postmenopausal period leads directly to changes in lipid metabolism: there is a shift from fatty acid oxidation towards fatty acid biosynthesis, which contributes to the accumulation of TGs and deterioration of liver function. Compensation of estrogen deficiency in women during peri- and postmenopause suppresses lipogenesis and gluconeogenesis, stimulates glycogen synthesis and β-oxidation of fatty acids in the liver [10].

Study results indicate the hepatoprotective effect of estrogens in the context of NAFLD development. A retrospective study of 368 postmenopausal women who received MHT for 12 months (75 — transdermal MHT, 293 — oral MHT) investigated the incidence of NAFLD after initiation of replacement therapy. After 12 months, the prevalence of NAFLD in the transdermal MHT group decreased from 24.0 to 17.3 %, and in the oral MHT group it increased from 25.3 to 29.4 %. However, in contrast to the transdermal MHT group, the oral MHT group showed significant reductions in total cholesterol and LDL-cholesterol and increases in HDL-cholesterol. Oral estrogen had a more pronounced positive effect on the lipid profile. Oral estrogen dosing regimen did not affect the progression of NAFLD and other chronic liver diseases. In subgroup analyses based on estrogen dose and progesterone type, there were no significant differences in the incidence of NAFLD progression between low-dose and standard-dose estrogen (7.1 % vs. 13.0 %; $p = 0.146$) or between natural and synthetic progesterone (14.5 % vs. 9.9 %; $p = 0.295$) [50].

Although standard doses of MHT do not appear to result in progression of NAFLD, selection of the lowest effective dose of estrogen is recommended for oral MHT, especially in women with pre-existing liver disease or high risk factors [50].

The positive effect of MHT on carbohydrate metabolism has been shown. Results of a systematic review and meta-analysis of 12 randomized controlled trials involving 1,412 patients with type 1 and type 2 diabetes mellitus demonstrate that MHT has a positive effect on glucose metabolism in the postmenopausal period. It is suggested that estrogens reduce insulin-mediated suppression of hepatic glucose production, which leads to a decrease in glucose levels in blood plasma. However, treatment efficacy depended on the route of estrogen administration. Transdermal MHT had no significant effect on either the change in glycated hemoglobin (mean difference: –0.34 %, 95% CI: –0.75–0.08; –3.66 mmol/mol, 95% CI: –8.1–0.85) or the change in fasting glucose (mean difference: –0.06 mmol/L, 95% CI: –1.09–0.97). At the same time, the oral MHT group demonstrated a decrease in the level of glycated hemoglobin (–0.61 %, 95% CI: –0.89 ÷ –0.32; –6.63 mmol/mol, 95% CI: –9.74 ÷ –3.52) and a decrease in fasting glucose levels (mean difference: –1.34 mmol/L, 95% CI: –2.03 ÷ –0.65). Since the transdermal route of administration allows the active substance to enter the systemic bloodstream directly, there is no "first pass" effect. The suppressive effect on gluconeogenesis is more pronounced with oral MHT due to first pass metabolism in the liver [51].

A systematic review of 7 studies found that MHT reduced insulin resistance in postmenopausal women regardless of dosage form. One study that directly compared the efficacy of oral and transdermal MHT demonstrated that oral MHT was more effective in reducing the risk of developing diabetes mellitus than transdermal therapy. Compared with no MHT, both forms of therapy were associated with reduction in glycated hemoglobin levels [49]. Enter your text here.

First pass through liver provides positive metabolic effects and improvement of lipid and carbohydrate metabolism during oral MHT. Notably, oral MHT in women aged 50–59 years was associated with a 31 % reduction in overall mortality compared with placebo (hazard ratio (HR) — 0.69; 95 % CI: 0.51–0.94) over 5–7 years of treatment and 18 years of follow-up after stopping MHT [52].

MHT and the risk of cholelithiasis

Data on the increased risk of developing cholelithiasis in the context of MHT are contradictory. In a randomized trial involving 22,579 women aged 50 to 79 years, therapy with conjugated equine estrogens or estrogens in combination with gestogens was associated with an increased risk of biliary tract disease and cholelithiasis [47]. However, oral MHT is a variety of drugs of different composition and dosage, and therefore it is incorrect to speak of an increased risk of cholelithiasis as a class adverse event.

Comparative data on the risks of cholelithiasis depending on the dosage form of the MHT product are limited. The randomized Women's Health Initiative trial and the prospective cohort Million Women Study compared transdermal estradiol with oral equine estrogens, but not oral estradiol. Both forms of MHT were associated with a slight increase in the risk of cholelithiasis during treatment [53, 54].

According to recent data, oral MHT is associated with the most favorable safety profile with regard to the risk of gallstone formation. The risk of cholelithiasis was assessed in a large retrospective cohort study involving 1.3 million women using population data from 2002 to 2019. 381,711 subjects received MHT, and 1,004,034 subjects didn't receive MHT. According to the study results, all types of MHT were associated with an increased risk of gallstone formation. The risk of cholelithiasis was adjusted for age group, body mass index, socioeconomic status, region, Charlson comorbidity index, parity, age at menarche, age at menopause, smoking, alcohol, physical exercise, period from menopause to inclusion into the study. Transdermal MHT was associated with the highest risk of developing cholelithiasis compared with other hormonal agents (4.4 %; HR — 1.602; 95% CI: 1.295–1.983). The average treatment duration in the transdermal estradiol group was 2 times shorter than in the group of oral fixed-dose combination MHT (Fig.). In addition, no statistically significant effect of any MHT on increasing the risk of gallbladder cancer has been demonstrated [55].

The study conducted a comprehensive analysis of different types of therapy, including the most common modern MHT in Russia, low-dose fixed combinations of estradiol and dydrogesterone (such as Femoston®), which were not associated with an increased risk of cholelithiasis according to high-quality RCTs [56]. The combination of low doses of estradiol and dydrogesterone was not associated with an increased risk of liver and gallbladder disease compared with placebo in a pooled analysis of three clinical studies (1,027 postmenopausal women aged 45 to 65 years). The mean

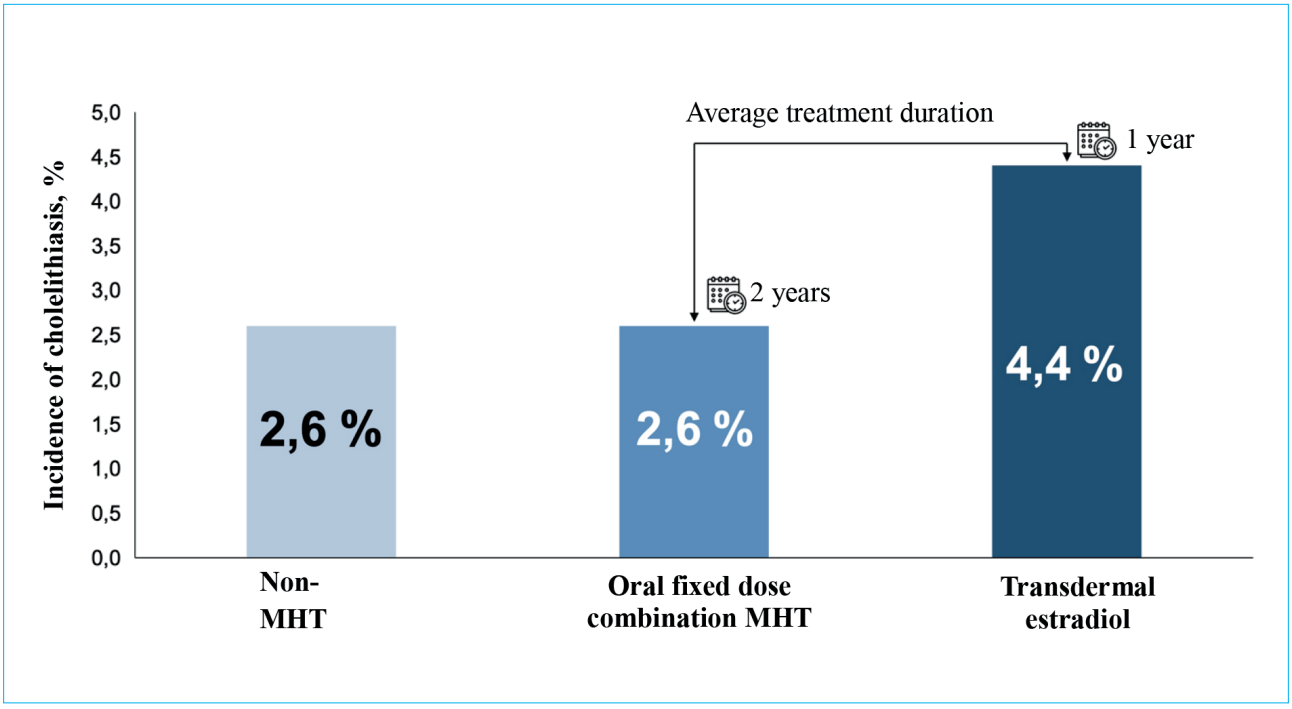

Figure. Risk of developing cholelithiasis depending on the type of menopausal hormone therapy (adapted from J.S. Yuk et al. [55])

Рисунок. Риск развития желчнокаменной болезни в зависимости от типа менопаузальной гормональной терапии (адаптировано по J.S. Yuk et al. [55])

treatment duration was 288.9 days in the estradiol and dydrogesterone group and 86.6 days in the placebo group. In all three studies, combination MHT was well tolerated in postmenopausal patients, with no increase in adverse events, including gallstones, compared with placebo [56–58].

Conclusion

The liver is one of the key organs that ensures the maintenance of normal metabolism. Estrogens have a significant effect on liver function, regulating carbohydrate, lipid and protein metabolism. As women age and enter menopause, estrogen levels decrease. Estrogen deficiency increases the risk of developing liver dysfunction, which can subsequently lead to NAFLD. This condition is associated with an increased risk of metabolic disorders, cardiovascular diseases, and higher mortality.

When choosing a medicinal product for MHT, it is important to select an agent with pronounced positive metabolic effects, the use of which is not associated with increased health risks. The principle of the minimum effective dose should be followed. The optimal option is oral forms of MHT, which provide a fixed dose of the hormone and do not require regular adjustments in most patients, unlike transdermal forms.

Oral combination MHT provides more pronounced metabolic effects and has a positive influence on lipid and carbohydrate metabolism in women during peri- and postmenopause. The advantages of oral MHT are related to the first-pass effect through the liver before the active substance enters the systemic circulation, which is not possible when using transdermal forms. Oral estradiol, passing through the liver, promotes the secretion of anti-atherogenic lipoproteins such as HDLs, while simultaneously reducing the levels of atherogenic LDLs and Lp(a). Normalization of the lipid profile, in turn, reduces the risk of developing atherosclerosis and cardiovascular diseases. In addition, oral administration of estradiol helps reduce insulin resistance. Normalization of carbohydrate metabolism and maintaining adequate blood glucose levels reduces the risks of metabolic syndrome and type 2 diabetes mellitus, which are associated with NAFLD development. Oral MHT reduces the risk of developing metabolic disorders and cardiovascular diseases, which also leads to a decrease in mortality. In addition, according to the latest data, oral combination MHT is associated with the lowest risk of developing cholelithiasis compared to other medicinal products.

Concerns about prescribing MHT to women with abnormal liver function test results are unfounded. Firstly, many patients initially have NAFLD (MAFLD), and modern agents for MHT, as argued above, are able to positively affect carbohydrate and lipid metabolism, inhibiting pathological processes leading to the progression of liver damage. Secondly, there is virtually no systematic data in the literature on the hepatotoxicity of estrogens and progestogens.

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