Interactions Between Preparations Containing Female Sex Hormones and Dietary Supplements

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Abstract

An increasing number of premenopausal women use contraception whereas postmenopausal women use hormone replacement therapy (HRT). This long-term hormone therapy poses a high risk of interactions with dietary supplements. Taking estrogens at the same time as selective estrogen receptor modulators (SERMs), biologically-active compounds of glycine soja, Ginkgo biloba or Pimpinella anisum, may distort the final effect of the hormone agent. On the other hand, estrogen therapy coupled with melatonin or retinol supplementation may lead to an increased level of dietary supplements in the serum as studies have proved a concomitant beneficial effect of HRT and vitamin E supplementation on lipid profiles. In turn, taking preparations containing St John’s wort during hormone therapy may lead to a reduction in hormone concentrations in serum and debilitation of the pharmacological effect. It results from the inductive effect of the biologically-active compounds of St John’s wort on the metabolism of hormones as a result of the enhanced activity of cytochrome P450 CYP3A4 ([Adv Clin Exp Med 2014, 23, 4, 657–663]).

Key words: dietary supplements, interactions, hormone replacement therapy, contraception.

Preparations containing a female sex hormone are mostly used by women at childbearing age as a method of contraception, or by postmenopausal women as a hormone replacement therapy (HRT). Although HRT is considered a risk factor of breast cancer and other diseases and though its use has declined [1, 2], it is still taken by a high percentage of women [3]. A HORTPOL 2002 study has shown that about 12% of Polish women aged 45–64 used HRT and 64% of them had it prescribed as an oral medication [4]. According to the Central Statistics Office, in 2009 about 30% of women aged 15–50 years and using birth control chose hormonal contraception via pills, patches, or injections [5]. Hormone therapy is constantly transforming in terms of doses, types of hormones, and schedule of their administration [6, 7]. Hormone replacement therapy or hormonal contraception are commonly continued for a long time. It can lead to the risk of an interaction not only with other drugs, but also with ingredients of dietary supplements. Dietary supplement usage is high and still increasing in many countries [8–10]. Their popularity varies depending on age, gender, living place, and educational level. Much more women than men take these preparations and also more women at the perimenopausal or postmenopausal age, especially with a higher educational level than younger women [11, 12].

The aim of this study was to review published studies concerning the interactions between drugs containing female sex hormones and dietary supplements.
**Estrogen Receptors and Selective Estrogen Receptor Modulators**

Estrogens act on the body via two subtypes of intracellular estrogen receptors, alpha (ERα) and beta (ERβ), which occur in different organs [13]. They function mainly as transcription factors but estrogen-regulated cells also contain membrane receptors linked to a protein G, which are responsible for rapid non-genomic estrogen activity. This signalization is also connected with, i.a., activation of Src kinases, PI3K/Akt kinases and MAPK/ERK, and stimulation of nitric oxide (NO) production by endothelial nitric oxide synthase (eNOS) [14–16].

Selective estrogen receptor modulators (SERMs) are a group of substances with estrogen-like effects. Among others, they include phytoestrogens, which occur naturally in some plants and are divided into three basic groups:

- isoflavones (found mainly in soybean, and in soy products),
- lignans (found in cereals, flax seeds, vegetables and fruits),
- coumestans (found in alfalfa sprouts and various kinds of beans) [17–19].

They differ from natural hormones in that they cause only a part of the estrogenic activity without showing other activities typical of these hormones. This is probably due to the different affinity of the two estrogen receptor subtypes (α and β), or from a differentiated structure of the ligand-estrogen receptor complexes, particularly differences in the structure of the trans-activating domains that occur during the binding of estrogen and SERMs [20, 21].

Phytoestrogens exhibit various estrogen-like effects, depending on cell type, target organ, endogenous estrogen concentration and receptor expression. These compounds exhibit a much higher affinity to the estrogen receptor beta than alpha. Phytoestrogens exert both positive and negative effects on the body. They can decrease the risk of development of many diseases, but also may interfere with the proper functioning of the reproductive system and can interact with medicines containing female sex hormones [21–23].

**Interactions Between Preparations Containing Female Sex Hormones and SERMs**

Soybean (Glycine hispida, Glycine soja) is one of the most important dietary sources of phytoestrogens. Its beans contain high amounts of isoflavones with estrogenic activity: daidzein, genistein and glycitein. Dietary supplementation of soy isoflavones may reduce menopausal symptoms and moreover breast cancer risk [24]. It has been shown that women taking a diet rich in soy protein (source of isoflavones) had significantly reduced urinary levels of the sex hormones estradiol, estrone and estriol, compared to women applying the conventional diet. Soy phytoestrogens reduce endogenous estrogen synthesis by inhibiting the activity of key enzymes involved in their metabolism – aromatase and dehydrogenases [25]. Suparto et al. [26] conducted a study with 40 monkeys administered an atherogenic diet for 15 months. The animals were divided into four groups: the first received casein as a protein source, the second – casein and hormone therapy (5 mg ethinyl estradiol + 1 mg of norethindrone per day), the third – soy protein providing 141 mg isoflavones per day, and the fourth – soy protein and hormone therapy. After a year of the study, myocardial infarction was induced in the animals. The heart necrosis area was significantly larger (55%) in the fourth group compared to the other groups of animals (approximately 30%). The mechanism of this interaction is unclear, but the authors suggest that it may be related to the adverse effect of soy isoflavones on cardiac hemodynamics, especially during hormone therapy.

An extract from the leaves of Ginkgo biloba (GBE) also contain phytoestrogens. Kaempferol, quercetin, and isorhamnettin are the most important flavonoids of G. biloba leave extract. Seung-Min et al. [27] investigated the estrogenic activity of these major components of GBE. They showed that the biologically-active compounds affected both the estrogen receptors α and β, but the affinity for ERβ was greater than for ERα. The results also suggest that these components induced pS2 gene transcription and PR (progesterone receptor) in MCF-7 human breast cancer. The authors suggest that the estrogen-like potential of the biologically-active compounds present in GBE can be used in the future as an alternative to hormone replacement therapy. However, further studies are needed to evaluate the physiological impact of GBE on estrogen receptors and possible interactions between hormone therapy and dietary supplements containing GBE.

Anise (Pimpinella anisum) is a plant whose fruits are used to give relief from abdominal pain, intestinal colic and flatulence due to their carminative, choleretic and antispasmodic activity. The main components of anise oil are trans-anethole, limonene, and estragole [28]. A study by Tabanca et al. [29] showed that an essential oil of Pimpinella
Female Sex Hormones and Dietary Supplements – Interactions

spp. fruits displayed estrogenic activity ranging from \(8.3 \times 10^{-8}\) to \(1.2 \times 10^{-6}\) (depending on plant species) as compared to 17β-estradiol. The median therapeutically-effective dose ranged from 45 mg to 650 mg. In vitro studies carried out by Kassi et al. [30] suggest that an aqueous extract of anise can also stimulate osteoblast differentiation and express antiestrogenic activity against breast cancer cells.

No studies have been conducted so far on the interaction between the active ingredients of ginkgo and anise and hormonal preparations (contraceptives, hormone replacement therapy). However, the same site of action of the hormones and compounds of these plants can lead to their interaction as a result of competition for the estrogen receptor, which can affect the expected effect.

Interactions Between Preparations Containing Female Sex Hormones and Other Components of Dietary Supplements

Melatonin

Melatonin is a biogenic substance the release of which is regulated by circadian rhythm. The amount of synthesized and released melatonin increases at night. It is involved in regulation of the sleep-wake rhythm and mood, and is implicated in causing a hypnotic effect through the activation of membrane-integrated melatonin receptors [31]. In Poland, melatonin has been available as an OTC drug prescribed in sleep disturbances caused by shift work, changing time zones or blindness. Currently it is also a component of dietary supplements. Components of hormonal contraceptives, e.g. estrogens, can increase serum melatonin concentration, which has been shown in clinical surveys conducted by Hilli et al. [32]. These authors observed that women taking oral contraceptives had an increased melatonin bioavailability: a 4–5-fold increase in the maximum concentration (\(C_{\text{max}}\)) and in the area under the curve (AUC). Elevated serum levels of melatonin had a negative impact on attention and concentration at work, and increased daytime sleepiness. Currently it is also a component of dietary supplements. Components of hormonal contraceptives, e.g. estrogens, can increase serum melatonin concentration, which has been shown in clinical surveys conducted by Hilli et al. [32]. These authors observed that women taking oral contraceptives had an increased melatonin bioavailability: a 4–5-fold increase in the maximum concentration (\(C_{\text{max}}\)) and in the area under the curve (AUC). Elevated serum levels of melatonin had a negative impact on attention and concentration at work, and increased daytime sleepiness.

The biologically-active components of St. John’s wort herb (Hypericum perforatum) may affect the pharmacokinetics of desogestrel, ethinyl estradiol and norethisterone. Heavy bleeding during the menstrual cycle as well as an increased risk of unwanted pregnancies were observed in women taking St. John’s wort preparations during hormone contraception [33–35].

Pfrunder et al [33] conducted a study among 17 healthy women using a contraception containing ethinylestradiol and desogestrel (20/150 mg/day) and preparation of St. John’s wort (900 mg/day). They observed breakthrough bleeding in 80% of the recruited women, while only 35% of the women had these adverse symptoms before the study. In addition, they found that supplementation with St. John’s wort altered the pharmacokinetics of 3-ketodesogestrel – the active metabolite of desogestrel, which was manifested by a reduction of \(C_{\text{max}}\) (about 23%) and AUC (about 42%), but had no effect on the bioavailability of ethinylestradiol [33].

In turn, Hall et al. [34] demonstrated changes in the pharmacokinetics of ethinylestradiol manifested in a reduced half-life of this hormone (23.4 h vs. 12.2 h). The authors also reported a decreased bioavailability of norethisterone expressed by increased clearance of the drug (8.2 l/h vs. 9.5 l/h). Serum concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH) and progesterone were unchanged. A major problem appeared to be breakthrough bleeding, which was the main reason for discontinuation of hormonal contraception among the respondents. In a study by Murphy et al. [35] conducted among 16 women using oral hormonal contraception, significant changes were observed in the pharmacokinetics of norethindrone and ethinylestradiol in the women taking 900 mg of St. John’s Wort extract/day. The authors reported a significant decrease in AUC and a significant increase in clearance of the analyzed hormones. In addition, three women had increased levels of serum progesterone (> 3 ng/mL), which was indicative of ovulation.

Vitamins and Other Antioxidant Substances

The rapid pace of life, overwork, bad eating habits and a stressful life are the most important factors influencing a large increase in the use of
The combined use of tocopherol acetate and fish oil increased the resistance of LDL to oxidation. This beneficial effect of dietary supplementation can be used to potentiate the positive effects of HRT on the lipid profile in postmenopausal women.

The level of sex hormone-binding protein (SHBP) increases, e.g., when using hormone therapy (HRT, contraception) and during oral combined administration of hormone contraceptives, especially with third generation progestagen and ethinylestradiol [42, 43]. Nayeem et al. [44] examined the relationship between diet, anthropometric and biochemical parameters and the concentration of SHBG in a group of 255 healthy premenopausal women (30–40 years). The authors showed a positive correlation between SHBG and HDL-cholesterol or progesterone as well as increased levels of SHBG during β-tocopherol and linoleic acid supplementation. Concomitant use of hormone therapy and β-tocopherol or linoleic acid supplementation may lead to an uncontrolled increase of SHBG concentration.

**Minerals**

Taking mineral supplementation during hormonal therapy may lead to mineral metabolism disturbances because hormonal contraception and hormonal replacement therapy can change mineral bioavailability. Akinloye et al. [45] conducted a study focusing on the influence of hormonal contraceptives on serum trace elements, phosphorus and calcium levels. The authors recruited 100 women using different contraceptive methods: 50 on oral contraception, 25 on injectable contraception and 25 on an intra-uterine method, and also 50 non-contraceptive users as a control group. They found significantly lower serum levels of zinc (0.70 vs. 1.00 mg/dL), selenium (74.52 vs. 89.68 µg/L), phosphorus (2.75 vs. 3.31 mg/dL) and magnesium (1.84 vs. 2.05 µg/L) in participants taking hormonal contraceptives than in the control group. However, the mean serum iron, copper (98.64 vs. 89.80, 1.69 vs. 0.98 µg/L) and calcium (2.43 vs. 2.10 mg/dL) concentrations were significantly higher in women taking hormonal contraceptives when compared with the control group. Beneš et al. [46] also found that hormonal contraception significantly increased blood copper concentration. Estrogens can lead to enhanced ceruloplasmin synthesis in the liver, which causes higher copper concentration in the blood. In Beneš’s study, in contrast to Akinloye et al. [49] observations, hormonal contraception did not influence blood selenium and zinc concentrations. Bureau et al. [47] conducted a study on 44 postmenopausal women.
Eighteen of them were treated with HRT, the remaining women were the control group. These authors observed higher mean plasma copper and chromium concentrations in the group of women using HRT than in the control group. They also found that urinary secretion of chromium, magnesium and zinc was decreased in the hormone-treated women group in comparison to the control group. Concomitant hormonal therapy and dietary supplementation with these minerals may lead to an uncontrolled increase of these elements' concentration.

**Summary**

A substantial increase in the number of women using hormonal preparations and frequent dietary supplementation poses a risk of interactions between hormones and the ingredients of dietary supplements. For effective and safe hormone therapy, it is important to achieve and maintain adequate serum hormone concentrations. A multitude of factors disrupting the balance of hormones, including nutritional factors, indicates the need for raising awareness on the interactions between hormones and components of dietary supplements. On the other hand, hormone therapy can also influence nutritional status, which has been observed in many studies. Knowledge of the mutual influence of hormones and dietary supplements should be continuously verified, mainly due to the emergence of an increasing number of studies. However, no studies have been conducted so far on the concomitant use of many ingredients of dietary supplements with hormones, so it is recommended rather to avoid the simultaneous intake of hormone preparations and dietary supplements.

**References**


Female Sex Hormones and Dietary Supplements – Interactions


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