1.1 Post-Menopausal Vaginal Hemorrhage Related to the Use of Hop-Containing Phytotherapeutic Products MenoCool® and Menohop®

Introduction

Vaginal bleeding is not uncommon in post-menopausal women and occurs in approximately 4–11 % of women who have reached menopause [1,2]. The incidence of bleeding appears to correlate with time since menopause, with the likelihood of bleeding decreasing over time [2]. Recurrence of bleeding is very common in the time immediately after menopause, being the 12 months of amenorrhea after what is currently defined as the final menstrual period, declining to low frequencies more than 3 years after the final menstrual period [2]. The differential diagnosis of bleeding in post-menopausal women can include endometrial cancer, polyps, leiomyomata uteri(fibroids) and infection, among others. Also endometrial hyperplasia may manifest clinically as uterine bleeding; however, since post-menopausal women should be estrogen deficient, endometrial hyperplasia at this time is abnormal and should be further investigated [1]. Post-menopausal hormone therapy can be a cause of endometrial hyperplasia and subsequent post-menopausal bleeding [3]. The last years the use of hormone-replacement therapy (HRT) has decreased. Many post-menopausal women often perceive phytoestrogens in food supplements as a safer alternative than HRT, because these products are 'natural' [4]. The use of these products is widespread [5]. In the Dutch market, many products are available with phytoestrogens obtained from various plants and foods. MenoCool® is a food supplement, containing hops, wheat, malt, oats and barley. In MenoHop® hopein from hop is combined with soy extract (Glycine max). Both products claim relieve of menopausal symptoms such as hot flushes and night sweats and can be purchased online in the web shop [6,7].

Reports

In the period from November 2011 till June 2017, the Netherlands Pharmacovigilance Centre Lareb received ten reports of postmenopausal vaginal bleeding caused by endometrial hyperplasia related to the use of the same hop-containing phytotherapeutic product (MenoCool®) and one report concerning soy and hop containing product Menohop®.

Table 1: Reports on MenoCool® and MenoHop®

Consumer, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction MedDra term	Time to onset, Action with drug outcome
A 130733 F, 61-70 years specialist doctor	Menocool® Menopausal symptoms		endometrial hyperplasia	month drug withdrawn recovering
B 130735 F, 51-60 years specialist doctor	Menocool® menopausal symptoms		postmenopausal haemorrhage	month drug withdrawn recovering
C 130736 F, 51-60 years specialist doctor	Menocool® menopausal symptoms		endometrial hyperplasia	month drug withdrawn recovering
D 157909 F, 61-70 years specialist doctor	Menocool® flushing		postmenopausal haemorrhage	1 year drug withdrawn unknown
E 178148 F, 51-60 years specialist doctor	Menocool® menopausal symptoms	progesterone cyclic	postmenopausal haemorrhage	2 years drug withdrawn recovering

F 181715 F, 51-60 years consumer	Menocool® menopausal symptoms	fexofenadine mometasone	vaginal haemorrhage abdominal pain endometrial hyperplasia	2 months drug withdrawn recovering
G 195247 F, 51-60 years consumer	Menocool® Menocool extra smelttablet®* hot flushes	alendronate	vaginal haemorrhage abdominal pain endometrial hyperplasia	5 months drug withdrawn recovering
H 228417 F, 51-60 years consumer	MenoCool® MenoCool extra smelttablet®*		vaginal haemorrhagie	1 year drug withdrawn, recovered/resolved
I 236497 F, 61-70 years consumer	MenoCool®		vaginal discharge endometrial hyperplasia painful breasts dry mouth muscle cramps	unknown drug withdrawn unknown
J 240723 F, 51-60 years specislist doctor	MenoCool® MenoCool extra smelttablet®*		Postmenopausal bleeding	3 years Drug withdrawn recovered
K 135168 F, 51-60 years specialist doctor	Menohop® menopausal symptms		postmenopausal haemorrhage	unknown

* Patients G, H and J received on the advice of the manufacturer Standby vital B.V. MenoCool® also additional melting tablets (2dd1) to reduce the complaint.MenoCool Extra® Melt Tablets contain extra non-estrogen-flavone extract (22mg), vitamin D3 (5mcg) and biotin (25mcg) [8].

Eight out of eleven patients recovered or were recovering after discontinuation with the supplement at the time of the reporting. From three patients, the outcome at Lareb is unknown.
Seven reports came from a gynecologist and four of the patients themselves. Also the women who have reported themselves were examined and treated by a gynecologist.

Patient A: a female aged 61-70 years, with endometrial hyperplasia following administration of MenoCool® for menopausal symptoms with a latency of days after start. The drug MenoCool® was withdrawn. The patient was recovering at the time of the reporting.

Patient B: a female aged 51-60 years was menopausal. Seven months after use of MenoCool® for menopausal symptoms, she got postmenopausal bleeding. A transvaginal echoscopy showed intra-myometrial myoma. The endometrium was 10 mm thick where the normal thickness in postmenopausal women should be 4mm. An endometrial biopsy showed proliferative endometrium without atypia or hyperplasia. The drug MenoCool® was withdrawn. She was treated with medroxyprogesterone. 6 weeks later the endometrial thickness was 3,9mm. The patient had no vaginal blood loss since.

Patient C: a female aged 51-60 years experienced 1 year after administration of Menocool® for menopausal symptoms endometrial hyperplasia. The supplement Menocool® was withdrawn. The patient underwent a hysteroscopic removal of an atypical endometrial polyp. The patient was at the time of the reporting recovering. The patient had no known medical history. She used a tibolon 2,5mg until September 2010.

Patient D: a female aged 61-70 years, experienced postmenopausal bleeding after 1 year use of MenoCool® for flushing. The drug MenoCool® was withdrawn. The patient outcome is unknown. Concomitant medication was not reported.

Patient E: a female aged 51-60 years experienced postmenopausal bleeding following 2 years of administration of MenoCool® for menopausal symptoms. Biopsy of the endometrium revealed weak endometrial proliferation which lead to the postmenopausal bleeding. She recovered after the

withdrawal of MenoCool®. Concomitant medication was progesterone. Previously the patient had spotting between menses during cyclic treatment with medroxyprogesterone.

Patient F had been using the MenoCool® (two times daily; morning one tablet, evening 0.5 tablet per oral administration) for hot flushes and vaginal dryness due to the menopause. At that time, she had not menstruated for 2 years but had experienced hot flushes for approximately 4 years. She had no medical history of vaginal complaints. After using MenoCool® for 2 months, the patient started to experience abdominal cramps and vaginal hemorrhage. The gynecologist diagnosed a high proliferation of the endometrium. The patient underwent a curettage. On the next appointment a significant increase in the endometrium was found again. The patient was treated with a course of norethisterone. Following withdrawal of norethisterone a heavy withdrawal bleeding had lasted for several days. The following control appointment showed proliferation of the endometrium again but still within the normal range; this time no action was deemed necessary. The patient ceased the use of the MenoCool® and had fully recovered .

***Patient G** had been using MenoCool® (1.5 tablets daily) for the indication hot flushes due to the menopause. She also bought the product online, through the same website as patient A. She had not menstruated for 5 years. She used also MenoCool Extra oral lyophilisate® (2 tablets daily) also a supplement from the same manufacturer, containing a nonestrogenic flavone extract. The patient started using MenoCool® in October 2014.The patient complained about abdominal pain/cramps . On advice of the manufacturer the MenoCool Extra oral lyophilisate® was added shortly after the start of MenoCool®. After 5 months using this combination, the patient experienced vaginal hemorrhage. She consulted a gynecologist. A cervix smear, internal examination, and ultrasound were performed. Due to the thickness of the endometrium, a pipelle endometrial biopsy was performed. Results showed no indication for cervix cancer. The use of MenoCool® was ceased and she had almost entirely recovered from the abdominal pain/cramps and vaginal hemorrhage.

***Patient H**: concerns a female aged 51-60 years, with menopausal vaginal hemorrhage used 1,5 tablet Menocool and 1 Menocool extra smelt tablet daily for hot flushes. After 1 year she experienced vaginal bleeding and mild abdominal cramps. On advise of the producer the MenoCool® extra smelt was withdrawn and she used it only occasionally in a lower dose. After 3 months she stopped the intake completely because of the persistent hemorrhage. The dosage of Menocool® was tapered down and finally stopped. The patient recovered after 10 days. Concomitant medication was not reported. The patient used not specified oral anticonception. After withdrawal the menstrual cycle did not return.

Patient I: concerns a 61-70 year old female with vaginal discharge, painful breasts, dry mouth, muscle cramps and endometrial hyperplasia following administration of Menocool® for hot flushes with an unknown latency after start. The Menocool® was withdrawn after 2 months of use. After withdrawal the patient got a vaginal bleeding. The patient has been referred to the gynecologist by her General Practitioner. The investigation showed an endometrial hyperplasia (10mm thickness).

***Patient J:** concerns a 51-60 years old woman who was already postmenopausal for 2 years and she used since 3 years MenoCool® and MenoCool Extra oral lyophilisate® to manage her menopausal symptoms. Because of the unexpected vaginal bleeding she was referred to the gynecologist. An ultrasound of the endometrium showed a 7,6mm thickness where endometrium biopsy revealed no abnormalities. The blood estrogen was 18pmol/l and FSH 40U/l. After withdrawal of both supplements she recovered within 1 month.

Patient K: a female aged 51-60 years, was already menopausal for 3 years. She experienced postmenopausal bleeding following administration of Menohop® for menopausal symptoms with unknown latency. An endometrial biopsy showed an atrophic endometrium with a normal smear. She also had two uterine myomas.

Other sources of information

On the website from the producer Standby vital B.V a possible estrogenic activity of the MenoCool® with the worsening of uterine mucosa and eventually resulting in menstrual bleeding has been mentioned. According to the manufacturer, this can be avoided by administering of the melting tablets MenoCool Extra® oral lyophilisate containing non-estrogenic flavones [6,8].

Ingredients MenoCool® per tablet weight: 1010 milligrams [6]

Ingredient	Quantity
Hop	41,40%
Nutritional fiber	9,90%
Buckwheat	8,48%
Black oat	8,48%
Malt	8,48%
Rogge	4,24%
Barley	4,24%
Wheat	4,24%
Maize	4,24%
Silicium	4,10%
Natural isoflavone complex	1,80%
Vegetable magnesium stearat	0,40%

Ingredients MenoHop® per capsule [7]

Ingredient	Quantity
Hope extract (humulus lupulus) standardized on hopein	200 mg
- 8-prenylnaringenine	200 µg
Soy extract (glycine max) standardized on isoflavones	50 mg
- Soy-isoflavones	20 mg

Literature

The effect of intake of isoflavones (a major class of phytoestrogens) from food supplements and histo(patho)logical changes in the endometrium of peri- and post-menopausal women has been investigated in several controlled trials.
Significant changes were reported in a controlled trial in which 376 subjects were randomized to receive either 150 mg isoflavones/day or placebo. After 5 years of treatment, six cases of hyperplasia (five cases of simple hyperplasia and one case of complex hyperplasia) were detected in the isoflavones group compared with none in the placebo group. No cases of endometrial carcinoma occurred during the 5-year period of the study [9].
Endometrial hyperplasia was also reported in a small randomized controlled trial in which 39 post-menopausal women were randomized to one of four treatment arms: low and high estradiol and low and high isoflavones. After 6 months, endometrial hyperplasia occurred in women from all groups. Missing a control group with only a placebo treatment and methodological flaws made this study less reliable [10].

A relationship between vaginal haemorrhagia and fyto-oestrogens from soy has been described by Chandrareddy *et al.* in case reports. Abnormal uterine bleeding with endometrial pathology was found in three women related to a high intake of soy products. The first woman had postmenopausal bleeding with uterine polyp, proliferative endometrium and a growing leiomyoma. The second woman presented with severe dysmenorrhea, abnormal uterine bleeding, endometriosis and uterine leiomyoma not responding to treatment. The third woman with severe dysmenorrhea, abnormal uterine bleeding, endometriosis and uterine leiomyomata presented with secondary infertility. All three women improved after withdrawal of soy from their diet [11].

On the other hand, a meta-analysis of 174 randomized-controlled studies on the safety of phytoestrogens revealed that the risk of vaginal bleeding, endometrial hyperplasia, endometrial or breast cancer malignancies has not been significantly increased in women using phytoestrogens compared to placebo or non-users [12].

Some of the cases received at The Netherlands Pharmacovigilance Centre Lareb were described earlier in case series published in 2012 and 2015 [13,14].

Mechanism

The three major classes of phytoestrogens found in typical human diets are isoflavones (such as genistein and daidzein), which are concentrated in soybeans and soy products, but are also found in other legumes; lignans, which are distributed in seeds, whole grains, berries, fruit, vegetables, and nuts; and coumestans, which are found in broccoli and sprouts [4].The flavonoid substance 8-prenylnaringenin (8PN, hopein) in hop also has phytoestrogenic properties. Of all phytoestrogens, 8-prenylnaringenin has the strongest estrogen receptor (ER) activity [15,16].
Phytoestrogens display estrogen-like activity since they are structurally similar to human estrogens and therefore they can bind to the estrogen receptor. In this way they are able to mimic or block the action of the human hormone estrogen, although they are much less potent [17]. In vitro assays have found that, although most phytoestrogens, including the isoflavones, bind both ERα and ERß and activate ER-dependent gene transcription through both subtypes [18]. Phytoestrogens can also manipulate steroid biosynthesis and transport by, for example, stimulating hormone-binding globulin (SHBG) synthesis in liver cells [19], and competitively displacing either 17 ß-estradiol or testosterone from plasma SHBG [20].
Isoflavones are ingested mainly as glucosides and are hydrolyzed by gut bacterial and mammalian enzymes, which releases the deglycosylated compounds daidzein, genistein and glycitein (among others). These may be absorbed or further metabolized by the gut bacteria to many specific (more potent) metabolites, including equol from daidzein and enterodiol. Once absorbed, isoflavones are extensively conjugated to glucuronides and sulfates in the liver and excreted in the bile or urine. Factors influencing absorption, distribution, metabolism and excretion of phytoestrogens include diet and gut microflora. In human subjects, even those on controlled diets, there is large interindividual variation in the metabolism of isoflavones, particularly in the production of equol [21].

Discussion and conclusion

Many women, concerned about the health risks of the synthetic hormones used in conventional hormone therapy (HRT), are looking for natural alternatives. They often perceive phytoestrogens in food supplements as a safer alternative [4]. It's important to know that these products are not necessarily safe because they are natural.

The supplements MonoCool® and MenoHop® are based on hop where the flavonoid 8PN the active phytoestrogenic substance is. Due to the estrogenic potency of 8PN, safety concerns arise for unrestricted long-term use as a herbal preparation without a drug status, and the need of further knowledge about positive and negative effects in vivo is obvious. The potency of 8PN must not be underestimated. Hop (Humulus lupulus L.) contains, besides 8-prenylnaringenin, other flavonoids, such as xanthohumol. Hop has been used for centuries as an essential ingredient for brewing beer and provides the typical aroma [17] However, the amount of 8-prenylnaringenin in beer is lower (up to 21 µg / l) than the declared content in MenoHop® (200 µg per capsule); Although the percentage of hops in MenoCool® is known (41.4%), the 8-prenylnaringenin content is not specified [7,8].

Preparations of hops that contain 8PN must be considered "estrogenic". However, no officially recognized standards exist yet for estrogenic formulations of hops [22].The use of dietary supplements with phytoestrogenic ingredients, such as hops (and soy), can possibly result in the development of endometrial hyperplasia and postmenopausal bleeding. Based on the described case reports to the Netherlands Pharmacovigilance Centre Lareb, we suggest a causal relation between vaginal bleeding due to endometrial proliferation after menopause associated with the use of this hop based products, containing 8-prenylnaringenin with the strong ER activity. It is not known whether the individual metabolic conditions may play a role in the occurrence of these complications.

The ingredients of the Supplement MenoCool Extra® melt tablets on the other hand are not specified non-estrogenic flavones and provide according to the manufacturer an anti-estrogenic activity. In case of vaginal bleeding the women are advised to add this preparation to their MenoCool® treatment and after recovering from the hemorrhage to continue this combined regime. It should be noted that this advice from the manufacturer can lead to dangerous situations in women with potential serious medical conditions seeking medical consultation too late.

Phytoestrogenic products MenoCool® and MenoHop® for relief of menopausal symptoms are available as over-the-counter preparations, and consumers often mistakenly believe that they do not cause

adverse drug reactions. Lareb advises to consider giving directions for better consumer information about these possible effects of phytoestrogens-containing food supplements.

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This overview was published on June 22, 2017. It is possible that in the meantime other information became available.