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(54) **METHOD FOR THE MANAGEMENT OF DYSMENORRHEA AND MENSTRUAL PAIN**

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(57) **ABSTRACT**

The present invention relates to a method for the management of dysmenorrhea involving administration of an estrogenic component which is preferably selected from the group consisting of estetrol and estetrol-like compounds. Estetrol-like compounds have been surprisingly found to be capable of mitigating dysmenorrhea, either when used alone or in combination with progestogenic components, and this to an extent surpassing the effect obtained with other compositions and with a favourable side-effect profile compared to currently available methods.

METHOD FOR THE MANAGEMENT OF DYSMENORRHEA AND MENSTRUAL PAIN

FIELD OF THE INVENTION

[0001] The present invention relates to a method of alleviating the symptoms of dysmenorrhea in a person, comprising administering to said person an effective amount of an estrogenic component. More particularly the estrogenic component is an estetrol component, as further defined herein, and the method enjoys a favourable side-effect profile compared to currently available methods.

BACKGROUND ART

[0002] Dysmenorrhea is a medical condition characterized by the presence of recurrent, crampy, lower abdominal pain that occurs during menses. Most women begin having dysmenorrhea during adolescence, usually within four to five years of the first menstrual period. Painful periods become less common as women age. For clinical purposes, dysmenorrhea is divided into two broad categories, primary and secondary dysmenorrhea. Primary dysmenorrhea refers to the presence of recurrent, crampy, lower abdominal pain that occurs during menses in the absence of demonstrable disease that could account for these symptoms.

[0003] Secondary dysmenorrhea has the same clinical features, but occurs in women with a disorder that could account for their symptoms, such as endometriosis, adenomyosis, or uterine fibroids.

Primary Dysmenorrhea

[0004] It is known that 50 to 90 percent of reproductive-aged women describe experiencing painful menstrual periods. The majority of these women are young and have primary dysmenorrhea. The prevalence of primary dysmenorrhea decreases with advancing age (Sundell G. et al.; *Br J Obstet Gynaecol* 1990; 97:588).

[0005] Primary dysmenorrhea has been associated with alterations in prostaglandin synthesis and metabolism. Prostaglandins released from endometrial sloughing at the beginning of menses play a major role in inducing contractions (Ylikorkala O, Dawood M Y.; *Am J Obstet Gynecol* 1978; 130:833).

[0006] The pain starts one to two days before or with the onset of menstrual bleeding and then gradually diminishes over 12 to 72 hours. It is recurrent, occurring in most, if not all, menstrual cycles. The pain is usually crampy and intermittently intense, but may be a continuous dull ache. It is usually confined to the lower abdomen and suprapubic area. Although the pain is usually strongest in the midline, some women also have severe back and/or thigh pain.

[0007] The severity of the pain ranges from mild to severe (Table 1 below) (Andersch B, Milsom I.; *Am J Obstet Gynecol* 1982; 144:655).

[0008] As used herein, the "dysmenorrhea symptoms grade" corresponds to the score obtained by applying the assessment presented in Table 1.

TABLE 1

Verbal multidimensional scoring system for assessment of dysmenorrhea

Grade	Working Ability	Systemic Symptoms	Analgesics
Grade 0: Menstruation is not painful and daily activity is unaffected	Unaffected	None	None required
Grade 1: Menstruation is painful but seldom inhibits normal activity; analgesics are seldom required; mild pain	Rarely affected	None	Rarely required
Grade 2: Daily activity is affected; analgesics required and give sufficient relief so that absence from school is unusual; moderate pain	Moderately affected	Few	Required
Grade 3: Activity clearly inhibited; poor effect of analgesics; vegetative symptoms (headache, fatigue, vomiting, and diarrhea); severe pain	Clearly inhibited	Apparent	Poor effect

[0009] It is important to note that there are no physical findings associated with primary dysmenorrhea and that primary dysmenorrhea is not associated with any laboratory abnormalities or abnormal findings on imaging studies. Diagnosis should therefore ascertain that the patient has no evidence of other disorders that could account for the pain. In particular disorders such as endometriosis, adenomyosis, fibroids, ovarian cysts, among others, have been associated with secondary dysmenorrhea.

Treatment Options for Primary Dysmenorrhea

[0010] Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered the first line of therapy (Proctor M, Farquhar C; *Clin Evid* 2003; :1994—Zhang W Y, Li Wan Po A.; *Br J Obstet Gynaecol* 1998; 105:780—French L.; *Am Fam Physician* 2005; 71:285).

[0011] NSAIDs should be started at the onset of menses and continued for the first one to two days of the menstrual cycle or for the usual duration of crampy pain. Patients with severe symptoms should begin taking NSAIDs one to two days prior to the onset of menses.

[0012] Combined Oral Contraceptive pills (COCs) can be given to patients who fail to respond to or cannot tolerate NSAIDs (Davis A R, et al.; *Obstet Gynecol* 2005; 106:97). COCs prevent menstrual pain by suppressing ovulation, thereby decreasing uterine prostaglandin levels. An additional mechanism may result from the reduction of menstrual flow after several months of use.

[0013] In a sexually active female, COCs may be considered for first-line of therapy because they serve a dual purpose: prevention of both pregnancy and dysmenorrhea.

[0014] A systematic review of randomized trials of estrogen-progestin contraceptive pills for treatment of primary dysmenorrhea reported a significant benefit of treatment (pooled OR of 2.99, 95% CI 1.76-5.07) (Wong C L, et al.; *Cochrane Database Syst Rev* 2009; :CD002120).

[0015] Few trials compared different doses of estrogen for treatment of primary dysmenorrhea; the review concluded pain relief was similar for low (≤35 mcg) and medium (>35 mcg) estrogen doses and there was no clear difference in efficacy among the different pill preparations.

[0016] However, additional data from observational studies and other randomized trials have demonstrated efficacy of very low dose estrogen pills for treatment of dysmenorrhea (Davis A R, et al.; *Obstet Gynecol* 2005; 106:97—Callejo J, et al.; *Contraception* 2003; 68:183—Winkler U H, et al.; *Contraception* 2004; 69:469—Endrikat J, et al.; *Contraception* 1995; 52:229—Hendrix S L, Alexander N J.; *Contraception* 2002; 66:393).

[0017] All these approaches relied on COCs employing synthetic estrogens such as ethinyl estradiol (EE), however. In such a case, there is a (dose dependent) risk of undesirable side-effects, such as thromboembolism, fluid retention, nausea, bloating, cholelithiasis, headache and breast pain.

[0018] Of particular importance is the fact that estrogens participate in the regulation of the synthesis of a variety of proteins in the liver, such as angiotensinogen, Sex Hormone Binding Globulin (SHBG), ceruloplasmin, Corticosteroid Binding Globulin (CBG), some coagulation factors, coagulation inhibitors or fibrinolysis markers. Changes in these haemostasis markers under the influence of strong estrogens such as EE may collectively contribute to create an imbalance between pro-coagulation and anti-coagulation factors which can enhance the risks of Venous ThromboEmbolism (VTE) events.

[0019] SHBG plasma levels are a reliable marker of the influence of an estrogen on the synthesis of these proteins by liver cells. This means that a correlation could exist between the level of SHBG induced by a specific COC and the risk of VTE associated with that COC (Odlind V, et al.; *Acta Obstet Gynecol Scand* 2002; 81:482).

[0020] Although cohort studies performed on a sufficient number of subjects are required to evaluate the risk of VTE with a specific COC, different haemostatic markers and carrier proteins (such as SHBG) can be measured to estimate this risk on a limited number of subjects.

[0021] There thus remains a need for a therapeutic approach which, on the one hand, has as little side effects as possible, but on the other hand proves very efficient in the management of dysmenorrhea.

SUMMARY OF THE INVENTION

[0022] The present invention relates to a method of alleviating the symptoms of dysmenorrhea in a person, comprising administering to said person an effective amount of an estrogenic component. More particularly the estrogenic component is an estetrol component, as further defined herein, and the method enjoys a favourable side-effect profile compared to currently available methods.

[0023] In one aspect of the method, one or more of the number, the frequency and the severity of treatment-related side effects is reduced, compared to other dysmenorrhea treatments of similar efficacy.

[0024] In one embodiment of the invention, the number, frequency and/or severity of VTE events is reduced, compared to other dysmenorrhea treatments of similar efficacy.

[0025] In another embodiment of the invention, no haemostatic change that exceeds the boundaries of the normal range, as further defined herein, occurs upon administration of the compositions of the invention.

[0026] In a further embodiment of the invention, the number, frequency and/or severity of headaches is reduced, compared to other dysmenorrhea treatments of similar efficacy.

[0027] In yet another embodiment of the invention, the number, frequency and/or severity of breast pain events is reduced, compared to other dysmenorrhea treatments of similar efficacy.

[0028] In one embodiment of the invention, the method involves the administration of an effective amount of an estrogenic component and of a progestogenic component.

[0029] In some embodiments of the invention, the estrogenic and the progestogenic components are included in a single dosage unit. In further embodiments, the dosage unit is a daily dosage unit.

[0030] In further embodiments, the progestogenic component is drospirenone and that component is used at a daily dose of from 0.5 mg to 10 mg, preferably at a daily dose of from 1 mg to 4 mg.

[0031] In yet further embodiments, the estrogenic component is used at a daily dose of from 1 mg to 40 mg, preferably at a daily dose of from 5 mg to 25 mg, even more preferably at a daily dose of from 10 mg to 20 mg. In particular embodiments, the estrogenic component is estetrol monohydrate.

[0032] In a specific embodiment of the invention, the estrogenic component is estetrol monohydrate at a daily dose of about 15 mg and the progestogenic component is drospirenone at a daily dose of about 3 mg.

[0033] The present method employs an estrogenic component which is a natural estrogen (i.e. found in nature) and a biogenic estrogen (i.e. occurring naturally in the human body).

[0034] Because biogenic estrogens are naturally present in the fetal and female body, a good tolerability and safety profile are observed, particularly if the serum levels resulting from the exogenous administration of such estrogens do not substantially exceed naturally occurring concentrations. A direct consequence of this good tolerability is the favourable side-effect profile obtained with the method of the invention compared to other methods.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0035] The term "estrogenic component" as used throughout this document encompasses substances that are capable of triggering an estrogenic response in vivo, as well as precursors that are capable of liberating such an estrogenic component in vivo when used in accordance with the present invention. In order for estrogenic components to trigger such a response they normally have to bind to an estrogen receptor, which receptors are found in various tissues within the mammalian body.

[0036] The estrogenic component of the present invention preferably is an estetrol component. The term "estetrol component", as used throughout this document, encompasses substances selected from the group consisting of estetrol, esters of estetrol wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; and combinations thereof. Even more preferably, the estetrol component is estetrol (including estetrol hydrates). Most preferably, the estetrol component contained in the dosage unit is estetrol monohydrate.

[0037] The term "progestogenic component" is defined as a substance that is capable of triggering a progestogenic response in vivo or a precursor which is capable of liberating such a substance in vivo. Usually progestogenic components are capable of binding to a progestogen receptor.

[0038] "About" as used herein referring to a measurable value such as a parameter, an amount, a temporal duration, and the like, is meant to encompass variations of +/−10% or less, more preferably +/−5% or less, even more preferably +/−1% or less of and from the specified value, in so far such variations are appropriate to perform in the disclosed invention. However, it is to be understood that the value to which the modifier "about" refers is itself also specifically disclosed.

[0039] The term "an effective amount" refers to an amount necessary to obtain a physiological effect. The physiological effect may be achieved by one dose or by repeated doses. In particular, "an effective amount" refers to an amount which is effective in reducing, eliminating, treating or controlling the symptoms of dysmenorrhea. The term "controlling" is intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or stopping of the progression of dysmenorrhea, but does not necessarily indicate a total elimination of dysmenorrhea, and is intended to include prophylactic treatment and chronic use.

[0040] As illustrated in Example 5, the present method of alleviating the symptoms of dysmenorrhea has proved surprisingly efficient despite the low daily dosage employed. Without wishing to be bound by theory, the present inventors believe that the superiority of the present method is in part due to the surprising effect of the estetrol component which is capable of mitigating dysmenorrhea on its own, as illustrated in the clinical results presented in Example 1.

[0041] It is indeed the case that while the administration of low doses of estrogen are known to decrease catamenial migraine, no such effect has ever been reported for dysmenorrhea. The uniqueness of the present finding that the estetrol component is capable of alleviating the symptoms of dysmenorrhea allows to decrease those symptoms when the estetrol component is administered alone according to the method of the invention. In one particular embodiment of the method, the estetrol component is administered alone during the progestin-free interval of the method of treatment according to the invention, as further described below.

[0042] This is all the more unexpected that a substantial number of scientific publications have characterized estetrol as a weak estrogen, therefore at the doses employed in the clinical trials reported in the examples it was not foreseen that such a positive effect on the management of dysmenorrhea symptoms would be observed.

[0043] Again without wishing to be bound by theory, the present inventors believe that the superiority of the present method is also due to the mild stimulatory effect that the estetrol component has on the endometrium, especially by comparison with the stronger stimulatory effect of ethinyl estradiol, which is the estrogen used in a large number of COCs. As a result, it was found that endometrial thickness was strongly diminished upon administration of the compositions of the invention. The thin endometrium contains relatively small amounts of arachidonic acid, the substrate for most prostaglandin synthesis. As a result of these changes in the endometrium, the compositions of the invention reduce both menstrual flow and uterine contractions at menses, thereby decreasing dysmenorrhea.

[0044] Besides, the method according to the invention was found to suppress ovulation in 100% of patients and suppression of ovulation is decreasing uterine prostaglandin levels.

[0045] In a comparative study, it was surprisingly found that a combination of estetrol with drospirenone as the progestogenic component was more efficient at managing the symptoms of dysmenorrhea than a combination of estetrol with levonorgestrel as the progestogenic component. This is illustrated by the results of the clinical trial reported in Example 2.

[0046] Another important benefit of the present estetrol component is derived from its relative insensitivity to interactions with other drugs (drug-drug interactions). It is well known that certain drugs may decrease the effectiveness of estrogens, such as ethinyl estradiol, and other drugs may enhance their activity, resulting in possible increased side-effects. Similarly estrogens may interfere with the metabolism of other drugs. In general, the effect of other drugs on estrogens is due to interference with the absorption, metabolism or excretion of these estrogens, whereas the effect of estrogens on other drugs is due to competition for metabolic pathways.

[0047] The clinically most significant group of estrogen-drug interactions occurs with drugs that may induce hepatic microsomal enzymes which may decrease estrogen plasma levels below therapeutic level (for example, anticonvulsant agents; phenytoin, primidone, barbiturates, carbamazepine, ethosuximide, and methosuximide; antituberculous drugs such as rifampin; antifungal drugs such as griseofulvin). The present estrogenic substances are not dependent on up- and downregulation of microsomal liver enzymes (e.g. P450's) and also are not sensitive to competition with other P450 substrates. Similarly, they do not interfere significantly in the metabolism of other drugs.

[0048] In particular, estetrol at a high concentration of 10 μmol/l does not inhibit (less than 10%) the major cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) unlike estradiol. Indeed, estradiol exerts a substantial inhibitory effect on CYP2C19 and CYP3A2 of 63% and 19%, respectively. Similarly, ethinyl estradiol, which is the estrogen used in a large number of COCs, exerts a substantial inhibitory effect on CYP2C19 and CYP3A4 of 82% and 45%, respectively.

[0049] The above observations serve to explain why the estetrol component of the invention hardly suffer from drug-drug interactions and thus produce a very consistent, i.e. predictable, impact. Thus, the efficacy of the estrogenic substances of the invention is highly reliable.

[0050] Additionally, the terminal half-life of the naturally occurring estrogens ranges from 2 to 14 hours while estetrol is characterized by a terminal half-life of 31.7 hours. Consequently, the use of estetrol in the method of the invention allows for a more than 24-hour coverage of the receptors by the treatment. This pharmacokinetic property enhances the efficacy of the product even in case of low treatment compliance by the user.

[0051] It has to be noted that when estetrol (E4) is associated with 3 mg drospirenone (DRSP) or 150 μg Levonorgestrel (LNG), the bleeding profile and the cycle control is improved in comparison to other combined oral contraceptives using a physiological estrogen, namely estradiol-valerate (E2V) or estradiol (E2).

[0052] In a study evaluating the bleeding pattern and cycle control of different E4/DRSP or E4/LNG combinations in comparison to a marketed quadriphasic combined oral contraceptive containing E2V and desogestrel (DSG), the combinations of 15 mg E4/DRSP and the combination 20 mg E4/LNG were both associated with a lower incidence of unscheduled bleeding/spotting days than the comparator. In addition, absence of withdrawal bleeding (also called amenorrhea) was much lower with the E4 containing preparations, particularly when E4 is associated with DRSP, than with the comparator. Finally, mean number of days with unscheduled bleeding/spotting by cycle was also lower with the combination of 15 mg E4/DRSP in comparison with the E2V/DNG preparation. This was also the case when compared to publicly available data on a marketed combined oral contraceptive containing E2 as estrogen in association with nomegestrol acetate (NOMAC).

[0053] Besides, the daily use of currently marketed estrogens (ethinylestradiol (EE), E2, E2V, conjugated equine estrogens) is associated with a dose-proportional increase in triglycerides levels. In the human body, high levels of triglycerides in the bloodstream have been linked to atherosclerosis and, by extension, the risk of heart disease and stroke. In the opposite to the currently available estrogens, E4 minimally increases triglycerides levels even at higher dosages.

[0054] Finally, the use of combined contraceptives have been associated with an increased risk in venous thromboembolic events (VTEs). In comparison with non-users, the use of second generation COCs multiply by 2 the risk of VTE and the use of 3rd and 4th COCs multiply the risk by 4. The absolute risk of VTE associated with the use of a specific combined contraceptive can only be assessed during very large epidemiological trials. However, and as requested by the European Medicinal Agency, several surrogate markers of the VTE risk can be measured in smaller clinical settings to estimate the risk.

[0055] As illustrated in Example 4, from the clinical results obtained with combinations of E4 and DRSP or LNG, the changes in the surrogate markers of VTE were minimal in comparison to the changes observed with Yaz® (a combination of 20 μg EE and 3 mg DRSP). DRSP is a fourth generation progestin associated with the highest risk of VTE when it is combined with the synthetic estrogen EE. Accordingly, the changes in the surrogate markers of VTE seen with a combination of EE and DRSP are substantial. In comparison, the changes observed with the E4 combinations are minimal even when DRSP is associated to the estrogen. For example, the SHBG plasma level changes observed when E4 was associated with 3 mg DRSP were considerably lower (mean percentage change of 7.9% for the 5 mg E4/3 mg DRSP group and of 44.5% for the 10 mg E4/3 mg DRSP group at treatment cycle 3) than the SHBG increases observed with a combination of 20 μg EE and 3 mg DRSP (mean percentage change of 306.3% for Yaz® at treatment cycle 3). The same positive pattern of change was observed with the 14 additional surrogate markers of VTE measured in this trial.

Methods of Treatment

[0056] The present methods usually employ uninterrupted oral administration of the estrogenic component and the progestogenic component during a period of at least 10 days, preferably of at least 20 days.

[0057] The term "uninterrupted" as used in here, means that the components are administered at relatively regular intervals, with no (therapeutically) significant interruptions. Naturally, minor interruptions may occur that do not affect the overall effectiveness of the present method, and indeed such aberrations are encompassed by the present invention. In a preferred embodiment, and more arithmetically, the administration regimen is deemed to be continuous if the longest interval between 2 subsequent administrations is not more than 3.5 times as long as the average interval. Even more preferably said longest interval is not more than 2.5 times, most preferably not more than 1.5 times as long as the average interval.

[0058] In the present method, the estrogenic and progestogenic components may be administered in separate dosage units. However, it is also possible and indeed very convenient to combine these two components into a single dosage unit.

[0059] In the method according to the present invention the combination of the progestogenic and estrogenic component is suitably administered uninterruptedly during a period of at least 10 days.

[0060] The invention may suitably be reduced to practice in the form of a variety of administration methods that are known to the person skilled in the art. Amongst these methods are the so called "combined" methods. The combined methods make use of monophasic preparations, which contain dosage units with a constant amount of an estrogen and a progestogen, or bi- or triphasic preparations which have varying levels of estrogen and progestogen; in most cases consisting of relatively constant levels of estrogen with a step-wise increase in progestogen throughout the cycle. The combined methods have in common that they are based on a regimen which involves an administration-free interval of about 7 days whereby withdrawal bleeding, simulating the natural menses, occurs. Thus 21 day intervals of hormone administration alternate with 7 days during which no hormones are administered.

[0061] In a preferred embodiment of the method of the invention, an administration-free interval of about 4 days is used. In this embodiment, a 24 day interval of hormone administration alternates with 4 days during which no hormones are administered. In yet another preferred embodiment of the method of the invention, a 24 day interval of hormone administration during which an estrogenic component and a progestogenic component are administered alternates with 4 days during which only an estrogenic component is administered (from day 25 to day 28).

[0062] As an alternative to the aforementioned combined methods, the so called "sequential" method has been proposed. Typical of the sequential method is that it comprises two consecutive phases, i.e. one phase during which estrogen and no progestogen is administered and another phase during which a combination of estrogen and progestogen is administered. The first sequential methods, like the aforementioned combined methods, made use of an administration free interval of about 7 days. More recently, sequential methods have been proposed which do not include an administration-free (or placebo) period, meaning that estrogen is administered throughout the full cycle and that progestogen is co-administered during only part of that cycle. WO 95/17895 (Ehrlich et al.) describes such an uninterrupted sequential method.

[0063] Yet another example of a method which is encompassed by the present invention is the so called "continuous combined" method, which is a particular version of the combined method that uses uninterrupted combined administration of a progestogenic and an estrogenic component during a prolonged period of time, e.g. more than 50 days. In contrast to ordinary combined and sequential methods, no regular menses occur in the continuous combined method as the continuous administration of progestogen in the indicated amounts induces amenorrhoea.

[0064] In one embodiment of the invention, which relates to the continuous combined method, the present method comprises the uninterrupted oral administration of the combination of the estrogenic component and the progestogenic component during a period of at least 28, preferably at least 60 days.

[0065] In one specific embodiment of the continuous combined method according to the invention, one tablet comprising the combination of the estrogenic component and of the progestogenic component is initially taken daily for at least about 24 consecutive days. Subsequently, e.g. during days 25 to 120, the patient may decide to take a tablet-free break of about 4 days. In any case, an about 4-day tablet-free break has to be taken after about 120 days of continuous tablet administration. After each tablet-free break, a new cycle starts with a minimum of about 24 days and a maximum of about 120 days of continuous administration.

[0066] In another embodiment of the invention, which relates to sequential and combined methods that employ a significant administration-free interval, the method of the invention comprises an interval of at least 2 days, preferably from 3-9 days, most preferably from 5-8 days, during which no progestogenic component and no estrogenic component is administered and wherein the resulting decrease in serum concentration of the progestogenic component and the estrogenic component induces menses.

[0067] Yet another embodiment of the invention, which concerns a sequential method without a significant pause, is characterised in that it comprises the uninterrupted oral administration of the estrogenic component during a period of at least 28 days, preferably at least 60 days, and in that, following the combined administration of the estrogenic component and the progestogenic component, the estrogenic component and no progestogenic component are administered during 3-18 consecutive days, preferably during 5-16 consecutive days and the resulting decrease in serum concentration of the progestogenic component should normally be sufficient to induce menses.

[0068] According to the present invention, the composition for use in a method of alleviating the symptoms of dysmenorrhea is capable of reducing the number, frequency and/or severity of adverse side effects including VTE, headache, breast pain, and the like, preferably including VTE, headache, and breast pain, more preferably including VTE and headache, and most preferably including VTE. The composition according to the present invention is particularly useful for effective treatment of the symptoms of dysmenorrhea while reducing the side effect of VTE at a significantly low frequency and severity.

[0069] In a particular embodiment of the invention, the method does not cause haemostatic change that exceeds the boundaries of the normal range. As used herein, "haemostatic change" is defined as the variation, upon administration of the compositions according to the invention, of the plasma level of one or more markers selected from: Sex Hormone Binding Globulin (SHBG), free tissue factor pathway inhibitor (free TFPI), free and total protein-S, protein-S activity, Corticosteroid Binding Globulin (CBG), Ceruloplasmin, antithrombin III, activated protein C (APC) resistance (e.g. APTT-based APCr or ETP-based APCr), Protein-C activity, D-dimer, Prothrombin, Prothrombin fragment 1+2, Factor VII, Factor VIII, von Willebrand factor, Factor II, PAI-1, tissue-type plasminogen (t-PA), plasminogen, E-selectin, and fibrinogen.

[0070] The above-listed markers are well-known to the skilled person and methods for the determination of their level are within the common general knowledge of the skilled person.

[0071] As used herein, the "normal range", when referring to levels of haemostatic markers, refers to the prediction interval that 95% of the population fall into.

[0072] In one embodiment of the invention, the method does not cause haemostatic change exceeding the boundaries of the normal range after one cycle of treatment, preferably the method does not cause haemostatic change exceeding the boundaries of the normal range after two cycles of treatment, even more preferably the method does not cause haemostatic change exceeding the boundaries of the normal range after three cycles of treatment.

[0073] In another particular embodiment of the invention, the method does not cause a change in the level of protein-S which exceeds the boundaries of the normal range.

[0074] In another particular embodiment of the invention, the method does not cause a change in the level of free TFPI which exceeds the boundaries of the normal range.

Compositions

[0075] The estrogenic component of the present invention preferably is an estetrol component, which encompasses substances selected from the group consisting of estetrol, esters of estetrol wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; and combinations thereof. More preferably, the estetrol component is estetrol (including estetrol hydrates). Most preferably, the estetrol component contained in the dosage unit is estetrol monohydrate.

[0076] The estetrol component of the invention may be used at a daily dose of from 0.1 mg to 100 mg. Preferably, the estetrol component of the invention is used at a daily dose of from 1 mg to 40 mg. Even more preferably, the estetrol component of the invention is used at a daily dose of from 5 mg to 25 mg. Still more preferably, the estetrol component of the invention is used at a daily dose of from 10 mg to 20 mg.

[0077] In a most preferred embodiment, the estetrol component of the invention is used at a daily dose of about 15 mg.

[0078] In other embodiments, dosages may be variable throughout the cycle (bi-phasic, tri-phasic or quadriphasic administration).

[0079] In a particularly preferred embodiment of the invention the pharmaceutical composition according to invention is designed for daily administration, i.e. it represents a daily dosage unit.

[0080] In the case of oral administration, the oral dosage unit according to the invention is preferably a solid or

semi-solid dosage form such as tablets, capsules, cachets, pellets, pills, powders and granules. The term "solid or semi-solid dosage form" also encompasses capsules that contain a liquid, e.g. an oil, in which the present estetrol component is dissolved or dispersed. Tablets and equivalent solid and semi-solid dosage forms can suitably contain materials such as binders (e.g. hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, other cellulosic materials and starch), diluents (e.g. lactose and other sugars, starch, dicalcium phosphate and cellulosic materials), disintegrating agents (e.g. starch polymers and cellulosic materials) and lubricating agents (e.g., stearates and talc). These tablets and equivalent solid and semi-solid dosage forms may be prepared by wet granulation, e.g. using an aqueous solution or an organic solution, as well as by direct compression.

[0081] Examples of progestogenic components which may suitably be used in accordance with the present invention include: levonorgestrel, norgestimate, norethisterone, dydrogesterone, drospirenone, 3-beta-hydroxydesogestrel, 3-ketodesogestrel, 17-deacetylnorgestimate, 19-norprogesterone, acetoxypregnenolone, allylestrenol, amgestone, chlormadinone, cyproterone, demegestone, desogestrel, dienogest, dihydrogesterone, dimethisterone, ethisterone, ethynodiol diacetate, fluorogestone acetate, gastrinone, gestodene, gestrinone, hydroxymethylprogesterone, hydroxyprogesterone, lynestrenol, mecirogestone, medroxyprogesterone, megestrol, mele,gestrol, nomegestrol, norethindrone, norethynodrel, norgestrel (including d-norgestrel, and dl-norgestrel), norgestrienone, normethisterone, progesterone, quingestanol, (17 alpha)-17-hydroxy-11-methylene-19-norpregna-4, 15-dien-20-yn-3-one, tibolone, trimegestone, algestone-acetophenide, nestorone, promegestone, 17-hydroxyprogesterone esters, 19-nor-17hydroxyprogesterone, 17alpha-ethynyltestosterone, 17alpha-ethynil-19-nortestosterone, d-17beta-acetoxy-13beta-ethyl-17alpha-ethynylgon-4-en-3-one oxime, 6beta, 7beta;15beta,16beta-dimethylene-3-oxo-17-pregna-4,9(11)-diene-21, 17beta-carbolactone or tanaproget and precursors of these compounds that are capable of liberating these progestogens in vivo when used in the present method.

[0082] Preferably the progestogenic component used in the present method is selected from the group consisting of progesterone, desogestrel, gestodene, dienogest, levonorgestrel, norgestimate, norethisterone, drospirenone, trimegestone, dydrogesterone, precursors of these progestogens and mixtures thereof

[0083] When the progestogenic component of the invention is drospirenone, it is preferably used at a daily dose of from 0.5 mg to 10 mg, even more preferably of from 1 mg to 4 mg. In a most preferred embodiment, the progestogenic component of the invention is drospirenone and it is used at a daily dose of about 3 mg.

[0084] When a different progestogenic component is used, the daily dose is adjusted such as to give the same pharmacological effect as a dose of 0.5 mg to 10 mg of drospirenone, preferably to give the same pharmacological effect as a dose of 1 mg to 4 mg of drospirenone.

[0085] In a preferred embodiment of the invention, the composition combines estetrol at a daily dose of from 5 mg to 25 mg with drospirenone at a daily dose of 0.5 mg to 10 mg.

[0086] In a more preferred embodiment of the invention, the composition combines estetrol at a daily dose of from 10 mg to 20 mg with drospirenone at a daily dose of 1 mg to 4 mg. In a yet more preferred embodiment of the invention, the composition combines estetrol at a daily dose of about 15 mg with drospirenone at a daily dose of about 3 mg.

[0087] In particular embodiments of the invention, the composition does not contain any added zinc salts. In these embodiments, no biocompatible zinc salts are used for the preparation of the compositions according to the invention.

[0088] The present invention has been described above with reference to a number of exemplary embodiments. Modifications and alternative implementations of some parts or elements are possible, and are included in the scope of protection as defined in the appended claims.

EXAMPLES

Example 1

[0089] During that study, healthy female subjects were treated for one 28-day cycle with either 10 or 20 mg E4 alone (n=10 and 11, respectively) or with a combination of E4 with either Progesterone (P) or Desogestrel (DSG) (n=15 or 16, respectively).

[0090] At baseline, occasional dysmenorrhea was reported by 11 subjects (21.2%), and frequent dysmenorrhea was reported by 19 subjects (36.5%). The distribution of dysmenorrhea is shown in Table 2 below. Overall, dysmenorrhea was reported by 25% to 53.3% of the subjects included in this trial.

TABLE 2

Reports at Baseline

	Number (%) of subjects			
Dysmenorrhea	10 mg E4 (n = 10)	20 mg E4 (n = 11)	20 mg E4/DSG (n = 15)	20 mg E4/P4 (n = 16)
No	4 (40.0)	7 (63.6)	5 (33.3)	6 (37.5)
Occasional	2 (20.0)	1 (9.1)	2 (13.3)	6 (37.5)
Frequent	4 (40.0)	3 (27.3)	8 (53.3)	4 (25.0)
Total number of subjects presenting dysmenorrhea at baseline	6 (60.0)	4 (36.4)	10 (66.7)	10 (62.5)

[0091] As shown in Table 3 of Treatment-emergent adverse events (TE-AE) below, reporting of dysmenorrhea during the treatment phase was low in comparison to the incidence recorded at baseline. Interestingly, E4 alone seemed to have a positive impact on the incidence of dysmenorrhea without any dose-related proportionality.

TABLE 3

Treatment-emergent adverse events

	Number (%) of subjects			
TE-AE	10 mg E4 (n = 10)	20 mg E4 (n = 11)	20 mg E4/DSG (n = 15)	20 mg E4/P4 (n = 16)
Dysmenorrhea	1 (10.0)	1 (9.1)	0	2 (12.5)

Example 2

[0092] In this clinical study comparing different doses and different combinations of estrogenic components and pro-

gestogenic components according to the invention, overall, at baseline, 68.9% of subjects had previously experienced dysmenorrhea, which was occasional in 40.4% of subjects and frequent in 28.5% of subjects.

[0093] As illustrated in Table 4 below extracted from Treatment-emergent adverse events (TE-AE) reported by at least 2 subjects in any treatment group, dysmenorrhea was more rarely reported when the progestogenic component was drospirenone than when it was levonorgestrel.

[0094] Additionally, and quite surprisingly, it is also seen in Table 4 that the lowest dose of the estrogenic component (15 mg daily) leads to fewer reports of dysmenorrhea as TE-AE than the higher dose (20 mg daily).

TABLE 4

Treatment-emergent adverse events

	Number (%) of subjects			
TE-AE	20 mg E4/ 150 µg LNG (n = 77)	20 mg E4/ 3 mg DRSP (n = 75)	15 mg E4/ 150 µg LNG (n = 80)	15 mg E4/ 3 mg DRSP (n = 79)
Dysmenorrhea	5 (6.5)	4 (5.3)	3 (3.8)	2 (2.5)

[0095] Finally, dysmenorrhea TE-AEs leading to discontinuation occurred once in each of the 20 mg E4 groups (1.3%) but did not occur in any of the 15 mg E4 groups (0%).

Example 3

[0096] In this clinical study comparing the combination of estrogenic component and progestogenic component according to the invention with a commercially available contraceptive treatment using also a natural estrogen (estradiol valerate at a 1, 2 or 3 mg dose of with dienogest at a dose of 0, 2 or 3 mg, marketed as Qlaira ® by Bayer HealthCare, Germany), the number of drug-related adverse events (Treatment-emergent adverse events (TE-AE) reported by at least 2 subjects in any treatment group) and the levels of the SHBG marker were monitored.

[0097] As illustrated in Table 5 below, 13 subjects (corresponding to 16.7%) reported TE-AEs related to headache in the treatment arm with the commercial product based on estradiol valerate and dienogest, while only 6 subjects (corresponding to 7.6%) did so in the group treated with a combination of 15 mg of estetrol and 3 mg of drospirenone. The number of events related to headache was thus shown to be much lower for the treatment according to the invention.

[0098] In addition, the number of adverse events related to breast pain was similar and very low (only 1.3% of occurrences) for the two treatments.

TABLE 5

Treatment-emergent adverse events

	Number (%) of subjects	
Drug-related adverse event	Qlaira E2V/DNG N = 78	15 mg E4/3 mg DRSP N = 79
Headache	13 (16.7)	6 (7.6)
Breast pain	1 (1.3)	1 (1.3)

[0099] In addition in this study, changes in SHBG concentrations were sequentially assessed at baseline and during Cycle 4 and Cycle 6 of administration of the combinations of E4/DRSP and E2V/DNG to women starting combined contraception (groups of patient called "Starters"). Women were defined as Starters when they had not used a hormonal contraceptive in the 3 months prior to randomisation. This "wash-out" period allowed to exclude patients whose SHBG levels were influenced by the previous COC used.

[0100] The results in terms of changes rom baseline are shown in Table 6 below.

TABLE 6

Mean percentage SHBG level changes from baseline to Cycle 4 and from baseline to Cycle 6

	Mean change from Baseline (%)	
SHBG level (Starters)	Qlaira E2V/DNG N = 22	15 mg E4/3 mg DRSP N = 30
Cycle 4/Screening	+43.9% (+/−35.6)	+27.1% (+/−12.1)
Cycle 6/Screening	+54.4% (+/−15.9)	+41.7% (+/−36.5)

[0101] As is apparent from Table 6, the method of the invention permits to minimize the SHBG level changes from baseline both at Cycle 4 and at Cycle 6, compared to a commercially available COC which also uses a natural estrogen.

Example 4

[0102] In this clinical study comparing two combination of estrogenic component and progestogenic component according to the invention with a commercially available contraceptive treatment (using ethinyl estradiol at 20 microg with drospirenone at 3 mg, marketed as Yaz ® by Bayer HealthCare, Germany), several haemostasis markers as well as carrier proteins were measured and changes from baseline to end of Cycle 3 in these parameters are presented below in Table 7.

TABLE 7

Mean (SD) percentage change from baseline to end of treatment Cycle 3 for haemostasis parameters and carrier proteins, in women using a combination of E4/DRSP or EE/DRSP

	Mean (SD) percentage change		
Parameters	5 mg E4/DRSP (n = 17)	10 mg E4/DRSP (n = 19)	20 µg EE/DRSP (n = 20)
Molecular markers			
D dimer	−25.9 (32.71)	−22.0 (29.70)	35.8 (56.14)
Prothrombin fragment 1 + 2	−24.1 (15.97)	−1.3 (28.63)	63.4 (50.21)
Group 1 coagulation inhibition			
Antithrombin III	1.6 (8.23)	1.5 (11.36)	−5.2 (7.88)
APC resistance (Rosing)	3.0 (26.19)	6.6 (37.45)	227.5 (181.27)
Protein S activity	8.6 (11.78)	52 (1029)	−27.4 (10.88)
Free TFPI	−13.5 (15.33)	−15.1 (8.89)	−46.6 (8.50)

TABLE 7-continued

Mean (SD) percentage change from baseline to end of treatment Cycle 3 for haemostasis parameters and carrier proteins, in women using a combination of E4/DRSP or EE/DRSP

	Mean (SD) percentage change		
Parameters	5 mg E4/DRSP (n = 17)	10 mg E4/DRSP (n = 19)	20 µg EE/DRSP (n = 20)
Group 2 coagulation inhibition			
Protein C activity	−3.7 (9.95)	−0.5 (10.18)	15.8 (13.82)
APC sensitivity (APTT)	0 (9.77)	−2.7 (8.88)	−9.8 (9.74)
Liver factors			
Fibrinogen	5.8 (12.24)	−0.6 (15.37)	19.5 (23.78)
Prothrombin	11.7 (34.71)	21.4 (24.98)	13.8 (21.76)
Endothelial factors			
Eselectin	3.2 (10.45)	−6.7 (14.00)	−19.5 (8.06)
tPA	−8.4 (25.76)	−15.7 (24.25)	−45.8 (14.05)
Carrier proteins			
CBG	17.1 (16.64)	28.1 (19.55)	170.3 (75.60)
SHBG	7.9 (26.25)	44.5 (34.12)	306.3 (117.70)
Ceruloplasmin	8.2 (12.24)	16.1 (11.14)	69.0 (22.93)

E4, estetrol;
EE, ethinylestradiol;
DRSP, drospirenone;
APC, activated protein C;
TFPI, tissue factor pathway inhibitor;
tPA, tissue type plasminogen;
CBG, corticosteroid binding globulin;
SHBG, sex hormone binding globulin.

[0103] A large difference was observed between DRSP combinations containing 20 microg EE and those with 5 or 10 mg E4: the procoagulant marker Prothrombin Fragment 1 +2 plasma levels were decreased with the different E4/DRSP combinations, whereas they increased with EE/DRSP (+63% from baseline to 3 months of use). These opposite results indicate that increase in the thrombosis marker Prothrombin Fragment 1 +2 is bound to the type (and dose) of estrogens (here EE vs. E4). Moreover, natural anticoagulants were unchanged (antithrombin III, protein S activity) or slightly decreased (free TFPI) by combinations containing E4 and typically decreased by EE/DRSP. While, as usual, activated partial thromboplastin time (APTT) related sensitivity to APC was almost unchanged with all preparations, the normalized APC sensitivity ratio was unchanged with E4 combinations whereas resistance to protein C was strongly increased by the EE/DRSP combination. Simultaneously to the non-increase of the procoagulant markers when using combinations of E4 and DRSP, there was a slight decrease in fibrinolysis parameters such as tPA and D-dimers levels.

[0104] With EE/DRSP combination, the increase in SHBG was important (+306%). All combinations of E4 (5, 10 mg) with DRSP showed a moderate increase in SHBG. Note that SHBG is considered as the most relevant biomarker for estrogenic impact of a COC on liver metabolism (Odlind V. et al.; *Acta Obstet Gynecol Scand* 2002; 81:482). CBG and ceruloplasmin are essentially synthesized under the influence of estrogens and are much less sensitive to the androgenic action ofprogestins. In the E4 and DRSP groups, increasing the dose of estrogen resulted in a slight increase from baseline for CBG and ceruloplasmin. However, by far the largest change from baseline was observed in the EE/DRSP group compared to the E4 treatment groups.

Example 5

[0105] A multicenter, placebo-controlled, randomised study to evaluate the benefits of the method of the invention on alleviating complaints of dysmenorrhea was conducted. The study population consisted in healthy female subjects, between 12 and 35 years old, inclusive (at the time of screening), with primary dysmenorrhea (onset<3 years post menarche).

[0106] The product according to the method of the invention was a combination tablet with estetrol (15 mg) and drospirenone (3 mg) administered orally once daily in continuous or 24/4-day regimen (i.e. 24 days of active tablets followed by 4 days of placebo tablets). Other doses of estetrol were included in supplementary arms, in addition to the placebo arm.

[0107] The efficacy of the method of the invention was demonstrated by following the change between baseline evaluation period and treatment evaluation period, primarily in the number of days with dysmenorrhea pain.

[0108] Dysmenorrhea pain was defined as pelvic pain during the menstrual/withdrawal bleeding episode and the 2 days before this episode.

[0109] Secondarily, the efficacy was followed by a daily scoring of dysmenorrhea pain, according to the following scale:

[0110] 0—No pain;

[0111] 1—Mild pain with no need for painkiller;

[0112] 2—Moderate pain with need for painkiller;

[0113] 3—Severe pain with need for painkiller.

[0114] Additional efficacy assessment were made as follows:

[0115] 1. Change Between Baseline Evaluation Period and End of Treatment Evaluation Period in Number of Days With Pelvic Pain Independent of Occurrence of Vaginal Bleeding;

[0116] 2. Change Between Baseline Evaluation Period and Treatment Evaluation Period in Number of Days With Pelvic Pain During Unscheduled Bleeding;

[0117] 3. Change Between Baseline Evaluation Period and Treatment Evaluation Period in Rescue Medication Use. Rescue medication use will be standardized intake of 200 mg Ibuprofen tablets;

[0118] 4. Percentage of Participants With Interference of Dysmenorrhea Pain With Work/School and Social or Other Activity;

[0119] 5. Percentage of Participants and Hours/ Days of Missing Time From Work Due to Dysmenorrhea Pain at Baseline, Month 3 and Final Examination (after Month 6);

[0120] 6. Percentage of Participants Satisfied With Study Treatment;

[0121] 7. Own Costs of Physiotherapy, Alternative Medicine, Acupuncture, Osteopathy, Medical Counselling, Massages, Herbal supplements/Teas per treatment of dysmenorrhea pain evaluated by completion of a Resource Use Questionnaire (converted to euros);

[0122] 8. Patient's improvement during the course of study as per The Clinical Global Impression Scale (CGI) completed by Investigators;

[0123] 9. Participants' Assessment in the Clinical Global Impression The Clinical Global Impression

Scale (CGI) as completed by the participants and rating their improvement during the course of the study;

[0124] 10. General Health, Body Pain, Physical and Social Functioning, Mental Health and Vitality as measured by General Health and Well-being Questionnaire SF-36 at Baseline, Month 3 and at Final Examination, using the SF-36 self-administered questionnaire, a general health status measure used to evaluate patient populations and to compare health status across different populations.

[0125] The clinical study demonstrates that the product according to the invention is effective in improving the symptoms of dysmenorrhea.

Example 6

[0126] A multi-institutional, placebo-controlled trial was conducted with collaborative randomized allocation double-blinded control for dysmenorrhea patients (primary dysmenorrhea patients, and secondary dysmenorrhea patients) aged 16 and older.

[0127] The study drug is a combination tablet containing estetrol (15 mg) and drospirenone (3 mg).

[0128] The tablet has two modes of administration:

[0129] for cyclic administration, the study drug was given orally in a cycle consisting of administration of one tablet per day at the same time every day for 24 days, followed by a 4-day discontinuation period;

[0130] for continued administration, the study drug was continuously administered, without discontinuation, in a dose of one tablet per day at the same time every day.

[0131] For primary evaluation, changes from baseline were scored at week 16 (4 cycles) according to the evaluation scale in Table 8 below.

TABLE 8

Dysmenorrhea score involving severity of dysmenorrhea as well as use of analgesics as reported in Harada T et al., Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial, Fertil Steril 2008; 90: 1583-1588

	Grade	Score	Details
Dysmenorrhea	None	0	none
(or nonmenstrual	Mild	1	some loss of work (or study) efficiency
pelvic pain)	Moderate	2	want to take some rest in bed, loss of work
	Severe	3	in bed more than 1 day
Use of analgesics	None	0	none
(previous or	Mild	1	take analgesics for 1 day
present period)	Moderate	2	take analgesics for 2 days
	Severe	3	take analgesics for >3 days

[0132] Additional efficacy assessments were made as follows:

[0133] 1. dysmenorrhea pain was evaluated by observing changes from baseline using a VAS scale and pelvic pain scores;

[0134] 2. occurrence of abnormal vaginal bleeding was evaluated;

[0135] 3. amelioration of premenstrual syndrome was evaluated by observing changes from baseline using a self-administered questionnaire;

[0136] 4. potential risk of the study drug on venous thromboembolism (VTE) was evaluated using surrogate markers of VTE (e.g., D-dimer, SHBG, protein C activity, and protein S activity);

[0137] 5. changes in the severity of lower abdominal pain, lower back pain, headache, vomiting, and a feeling of sickness during menstruation;

[0138] 6. changes in endometrial thickness from baseline;

[0139] 7. serum CA125 concentration, and serum C reactive protein concentration;

[0140] 8. serum estradiol concentration, and serum progesterone concentration;

[0141] 9. safety items:

[0142] adverse events;

[0143] clinical test results (including an endocrine test), vital signs;

[0144] uterine size.

[0145] The clinical study demonstrates that the product according to the invention is effective in improving the symptoms of dysmenorrhea.

1-17. (canceled)

18. A method of alleviating the symptoms of dysmenorrhea in a person in need thereof, comprising orally administering to the person an effective amount of an estetrol component.

19. The method of claim **18**, further comprising orally administering to the person a progestogenic component.

20. The method of claim **19**, wherein the estetrol component and the progestogenic component are administered in the same composition.

21. The method of claim **20**, wherein the composition is an oral dosage unit providing a daily dose of the estetrol component and the progestogenic component.

22. The method of claim **19**, wherein the progestogenic component is selected from progesterone, desogestrel, gestodene, dienogest, levonorgestrel, norgestimate, norethisterone, drospirenone, trimegestone, dydrogesterone, precursors of these progestogens, and mixtures of any thereof.

23. The method of claim **19**, wherein the progestogenic component is drospirenone.

24. The method of claim **18**, wherein the estetrol component is administered at a daily dose of from 1 mg to 40 mg.

25. The method of claim **18**, wherein the estetrol component is administered at a daily dose of from 5 mg to 25 mg.

26. The method of claim **19**, wherein the drospirenone is administered at a daily dose of from 0.5 mg to 10 mg.

27. The method of claim **19**, wherein the drospirenone is administered at a daily dose of from 1 mg to 4 mg.

28. The method of claim **18**, wherein the estetrol component is estetrol monohydrate.

29. The method of claim **18**, wherein the estetrol is administered at a daily dose of about 15 mg.

30. The method of claim **29**, further comprising administering drospirenone at a daily dose of about 3 mg.

31. The method of claim **18**, wherein the method is effective to improve dysmenorrhea symptoms after 10 days of daily administration.

32. The method of claim **31**, wherein the method is effective to improve the person's dysmenorrhea symptoms grade by at least one unit.

33. The method of claim **18**, wherein the persons' haemostatic changes do not exceed the boundaries of a normal range after daily administration for one menstrual cycle of at least 28 days.

34. The method of claim **18**, wherein the method comprises an administration-free interval of about 7 days.

35. The method of claim **18**, wherein the method comprises an administration-free interval of about 4 days.

36. The method of claim **19**, comprising a 24-day interval during which the estetrol component and progestogenic component are administered, alternating with a 4-day interval during which only the estetrol component is administered.

* * * * *