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RESEARCH ARTICLE

Phyto-progestins for the treatment of abnormal uterine bleeding without organic cause in women at high risk for breast cancer and breast cancer survivors: a prospective, pilot study

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ABSTRACT

Objectives: Some plants, such as Dioscorea Villosa (DV), Vitex Agnus Castus (VAC) and Turnera diffusa (D) have some 'progesterone-like' properties. We have investigated their simultaneous administration in breast cancer (BC) survivors or carriers of specific genetic mutations that can increase the risk of developing BC suffering from abnormal uterine bleeding without organic cause.

Methods: Women with irregular cycles in terms of length (interval between ≤ 24 or ≥ 38 days) without a uterine organic disease (polyps, adenomyosis, fibroids, hyperplasia/malignancy) were included. A daily diary of bleeding, questionnaires about health-related quality of life (Short Form 36) and menstrual psychophysical well-being (PGWB-1) and the Greene Climacteric Scale (GCS) (in women older than 40 years old) questionnaire were used. The presence of some premenstrual syndrome (PMS) symptoms was also evaluated.

Results: In the analyzed group of women ($n=15$), all experienced a regularization of the menstrual cycles, with a mean duration in the three months of use of 27.1 ± 3.2 days, with a significant reduction of menstrual pain ($p=0.02$) and flow ($p=0.02$) intensity. Women with PMS (7/15) reported an impovement in depression, headache and abdominal pain scores ($p<0.05$). No specific deterioration of different questionnaires evaluated during treatment were observed. General satisfaction with the treatment was 6.8 ± 0.3/10 on a 10 point.

Conclusions: A combination of DV, VAC and D could be a promising candidate to treat menstrual irregularities without an organic cause, with a significant reduction of menstrual pain and flow intensity and possible additional benefits in PMS symptoms treatment in women at genetic risk for BC and BC survivors.

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Background

Progesterone is a natural steroid hormone produced by the corpus luteum once the oocyte is released by the ovary; then, its levels start to increase in the secretory phase of the menstrual cycle, and if there is no fecundation, they naturally decline [1]. The importance of progesterone in the whole women life lies in its properties: it promotes regular menstrual cycles, it reduces uterine contractions during menstrual flow and the intensity of bleeding, it speeds up the general metabolism, it increases the quality of sleep, it prepares the endometrium for implantation, it ameliorates the mood during pregnancy and it plays a beneficial role in the premenstrual symptoms [2].

There is evidence to support that some plants, such as Dioscorea Villosa, Vitex Agnus Castus and Damiana (Turnera diffusa var. aphrodisiaca) – also known as phyto-progestins – have properties that can simulate progesterone activities. In particular, a molecule called Diosgenin is taken from the roots of Dioscorea and is the 'progestational substance' that was studied in 1944 by Russel Marker to introduce the first contraceptive pill [3].

Nowadays, Diosgenin is used as a precursor of endogen progesterone and of dehydroepiandrosterone (DHEA). Therefore, Diosgenin is useful for premenstrual syndrome (PMS) and menopausal neurovegetative symptoms treatment [4]; moreover, Diosgenin also has some anti-ageing effects, decreasing the health risks linked to cardiovascular disease [5], osteoporosis [6] and diabetes by inhibiting the production of pro-inflammatory cytokines [7]. Recently, Diosgenin has also been studied for its capability in contrasting the pharmacological resistance of cancer cells to treatments [8].

Vitex Agnus Castus contains many active substances such as flavonoids, and this explains its role in regulating menstrual cycles (in terms of oligomenorrhoea and dysmenorrhea) and in contrasting premenstrual symptoms. Vitex Agnus Castus is a dopamine agonist, so it can improve breast tenderness [9], and it can be used against mild hyperprolactinemic disorders [10]. Also, it can reduce neurovegetative climacteric symptoms – by promoting β-endorphin and melatonin synthesis [11] – and the ones related to PMS [12]. In particular, Vitex Agnus Castus efficacy has been proven to lower the number of headache attacks

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in a high percentage of women who had taken it for at least 3 months [13].

The third plant with proposed phyto-progestin activities is Damiana, which has a weak progestinic activity [14], resulting in its aphrodisiac, diuretic and anxiolytic properties [15], though the evidence on these effects is only preliminary and limited.

Rationale

There are some women that have specific contra-indications to the use of synthetic hormones (like progestins), such as breast cancer survivors. Moreover, there are situations in which there is a concern to prescribe synthetic hormones: we refer to women who are carriers of specific genetic mutations that can increase the risk of developing breast cancer (such as BRCA 1 and 2 and other specific genes) [16]. The risk of breast cancer occurrence in BRCA1 patients is 20% after 40 years of age, increases to 51% after 50 years and goes to 85% after 70 years. For BRCA2, the percentages are 28% after 50 years of age and 84% after 70 years [17].

The combination between Dioscorea, Vitex Agnus Castus and Damiana, acting on different pathways and mimicking the effect of natural progesterone as shown before, could be an interesting approach for the medical management of menstrual disorders in breast cancer survivors or in women with genetic mutations that predispose them to breast cancer. Our interest toward these natural molecules is due to the fact that there was no literature about their possible use in breast cancer survivors, while similar studies were recently performed for phytoestrogens [18]. Thus, we have decided to investigate their simultaneous administration in women with irregular cycles in terms of length (interval between one cycle to another ≤ 24 days or ≥ 38 days) without a uterine organic disease (polyps, adenomyosis, fibroids, hyperplasia/malignancy).

Materials and methods

Design of the study

This was a pilot, prospective, independent, single-group, monocenter, daily-diary-based trial conducted between April 2021 and December 2022 in the Modena Family Cancer Clinic of the Azienda Ospedaliero-Universitaria of Modena. The study was designed and conducted in full accordance with the World Medical Association Declaration of Helsinki, 2002 revision, and all of the women gave their informed consent to the anonymous use of their data for research purposes.

Subjects

The inclusion criteria were as follows:

- Abnormal Uterine Bleeding in terms of cyclicity (interval between one cycle to another ≤ 24 days or ≥ 38 days) [19];
- Women aged between 18 and 55;
- Women with germinal BRCA mutations or others mutations related to inherited predisposition for breast cancer (such us RAD 50, PALB 2, etc.), including breast cancer survivors;
- Women with endometrial (E) or ovulatory (O) disfunction according to COEIN category of FIGO classification system (PALM-COEIN) [19].

Exclusion criteria

- Women looking to get pregnant;
- BMI < 18 kg/m^2 or > 35 kg/m^2;
- Decompensated thyroid disease;
- Transvaginal ultrasound-based (TV-US) diagnosis of organic diagnosis of PALM categories for uterine bleeding (polyps, adenomyosis, fibroids, malignancy/hyperplasia) [19]

Some included women were also suffering from premenstrual syndrome (PMS) according to the American College of Obstetricians and Gynecologists (ACOG) definition of PMS [20]; however, this was not a mandatory criterion for the inclusion in this prospective study.

The most common symptoms considered were depression, irritability, anxiety, insomnia, headache, abdominal pain and breast tenderness. ACOG recommends the diagnosis of PMS when:

- symptoms are present in the 5 days for a period for at least three consecutive menstrual cycles;
- symptoms end within 4 days after a period starts;
- symptoms interfere negatively with normal daily activities [20].

Study drugs and evaluations

Visit 1 (enrolment)

Basal characteristics were collected together with the genetic mutation details and TV-US performed (Uterine size, endometrial thickness and ovary size), in order to exclude organic causes of irregular cycles (PALM category sec. FIGO classification system). The causes of COEIN not in the inclusion criteria (Coagulopathy, iatrogenic and not otherwise classified) were investigated by performing an accurate medical history and analyzing eventual previous blood exams performed by the patients. The daily diary of bleeding and pain (1–60 days: before treatment cycles, 60–150 days: treatment cycles) was assigned. No specific endocrine evaluations were performed to assess endometrial and ovulatory disfunctions, but they were investigated by observing the patient menstrual diary, nor specific endometrial histological evaluations. Patients filled out questionnaires about health-related quality of life (QoL) (Short Form 36) and related to the menstrual psychophysical well-being (PGWB-1). Moreover, women over 40 years old were asked to fill in the Greene Climacteric Scale (GCS) questionnaire. The presence of PMS, according to the American College of Obstetricians and Gynecologists (ACOG) definition of PMS, was verified (visual analogue evaluation of each symptom: depression, irritability, anxiety, insomnia, headache, abdominal pain and breast tenderness). At this point, we gave three packs of Progepril® to our patients, instructing them to take 2 pills of Progepril® per day for 14 days from the 14th day after the next menstrual bleeding for three consecutive cycles.

Visit 2 (about 5 months after Visit 1)

The completed daily diary of bleeding and pain (1–150 days) was collected, and the patient's satisfaction with the treatment (with a visual analogue scale from 0 to 10) and any adverse/beneficial events were recorded. Questionnaires on health-related QoL (SF36), on to the menstrual psychophysical well-being (PGWB-1)

and on climacteric symptoms – only for women over 40 years old – (GCS) were repeated. Women with PMS were investigated regarding the intensity of their PMS symptoms (visual analogue evaluation of each symptom: depression, irritability, anxiety, insomnia, headache, abdominal pain and breast tenderness).

The women included were required to complete a diary card on a daily basis, including information about daily bleeding (none, mild, moderate, intense), pelvic pain (none, mild, moderate, intense) and the number of pain-killers taken per day.

Study drug

Women were treated with Progepril® (Named srl, Lesmo (MB), Italy) that contains 300 mg of Dioscorea Villosa roots, 200 mg of Vitex Agnus Castus plant and 200 mg of Damiana bid for 14 days from the 14th day after menstrual bleeding.

Statistical analysis

Data analysis

Statistical analysis was performed using the statistical package StatView (version 5.01.98, SAS Institute Inc., Cary, NC). The within-group comparison was performed using the t-test for paired data and using the Wilcoxon signed-rank test for normal and non-normal data distribution, respectively. For all analyses, the null hypothesis was rejected at two-tailed p-value > 0.05. Results are expressed as the mean ± standard deviation (SD).

Results

A total of 21 women were eligible, and they were asked to participate in the study. Of these, 21/21 (100%) subjects accepted, signed the informed consent and were then included in the study. Six of twenty-one (28.6%) women were lost to follow-up, leaving the women to be analyzed at 15/21 (71.4%). Two women were excluded for not completely executing the study questionnaires and the lack of data for study analysis. Four women discontinued the use of the study drugs before the end of study follow-up, two for consent withdrawl, one for reported side effects (nausea and vomiting) and one for the occurrence of ovarian cancer (a BRCA1 mutation carrier at 50 years old).

The baseline features of the women included in the final analysis are reported in Table 1; four of them were breast cancer survivors (4/15, 26.7%).

All women included with irregular cycles, according to our inclusion criteria, (15/15, 100%) experienced a regularization of the menstrual cycles, with a mean duration in the three months of use of 27.1 ± 3.2 days, both in women < ($n = 4$) and ≥ 40 ($n = 11$) years of age.

The menstrual pattern was ameliorated and pain was reduced: we have recorded a significant reduction of menstrual pain ($p = 0.02$) and flow ($p = 0.02$) intensity (measured by points per day of flow) (Table 2).

In 7/15 (46.7%) women with PMS, a clear reduction in symptoms was reported; they were all the youngest women (range: 29–41) ($p < 0.001$) in the study except one of them aged beteween 45–54 years old.

Specifically, patients with PMS reported an impovement in depression, headache and abdominal pain scores ($p < 0.05$ for specific VAS scores).

No significant changes were observed for body weight (71.4 ± 4.7 to 71.9 ± 4.8 kg, $p = 0.58$) during treatment.

No specific deterioration of Health-related QoL (SF-36 questionnaire), Psychological General Well-Being Index (PGWB) and Greene Climacteric Scale in women older than 40 years ($n = 10$) during treatment were observed as reported in Table 3. Satisfaction with the treatment in general was 6.8 ± 0.3/10 (range: 5–8) on a 10 point Visual Analogic Scale (VAS).

Table 1. Baseline features of the subjects included in the study. Values are expressed in mean ± standard deviation (SD).

	Subjects ($n = 15$)
Age (years)	42.4 ± 6.2 (29–51)
Weight (Kg)	67.5 ± 9.5 (55–87)
Previous breast cancer (%)	4/15 (26.7%)
Genetic mutation	
BRCA 1	5/15 (33.3%)
BRCA 2	7/15 (46.7%)
Other	3/15 (20.0%)

Discussion

Even with our small sample of treated subjects, the results from this pilot study about phyto-progestin use for the treatment of abnormal uterine bleeding without organic cause in women at high risk for breast cancer and breast cancer survivors are promising.

As it is well known, progestins are used to regulate menstrual cycles and decrease heavy menstrual bleeding symptoms in young and perimenopausal women [21]. Women suffering from abnormal uterine bleeding do not have cyclic production of progesterone [22], so cyclic progestins are the first line of treatment in menstrual disorders and heavy menstrual bleeding [23].

Focussing on the regularity of menstrual cycles, all of our patients experienced a regularization of their menstrual cycles (100%), irrespective of their age/basal features. Moreover, it seems that this combination is also able to reduce spotting episodes, with a significant effect on menstrual flow intensity. Such preliminary observations are very important since the conflicting data that correlate the risk of breast cancer during synthetic progestins use [23].

In addition, other very promising data are about the significant effect on menstrual pain. In a recent systematic review and meta-analysis, Iwata et al. demonstrated that progestins in a continuous regimen are more effective in treating dysmenorrhea than combined hormonal contraceptives (CHCs) with a low dose of estrogens [24] since progesterone/progestins can strongly reduce uterine contractions. Our combination of phyto-progestins has the advantage to reduce menstrual pain in three months of observation, showing that they can be safely used to treat even breast cancer survivors suffering from dysmenorrhea.

Last, but not least, we observed satisfaction regarding symptoms related to PMS, especially in the youngest women included (<40 years old). Progesterone is probably the causal factor of the mood symptoms experienced by the women with PMS. In particular, synthetic progestins are the cause for the changes in mood that have been noticed by some users of synthetic CHCs [25]. In this view, it could be possible that phyto-progestins can act in different ways compared to synthetic progestins, that result in beneficial improvements to luteal mood changes. In relation to premenstrual migraines, Warhurst et al. conducted a meta-analysis showing that progestin-only pills (POP) reduced the number of migraine attacks in a month, but the small effect size may reflect the variability in treatment response between women [26]. With regard to climacteric symptoms, progestins

Table 2. Baseline and after treatment characteristics of bleeding and pain characteristics during Menstruation.

	Baseline cycle ($n=15$)	Mean of 3 cycles of treatment ($n=15$)	p-value
Cycle length (days)	Irregular	27.1 ± 3.2	/
Menstrual flow length (days)	4.86 ± 0.30	5.14 ± 0.34	0.40
Menstrual flow intensity (points per day of flow)	1.91 ± 0.14	1.60 ± 0.10	0.02
Menstrual pain intensity (points per day of flow)	1.81 ± 0.19	1.30 ± 0.12	0.02
Number of painkillers taken	1.1 ± 0.36	0.59 ± 0.23	0.07

Table 3. Baseline and after treatment characteristics of Short Form 36 questionnaire (with specific domains), of Green Climacteric Scale (with specific domains) and the Psychological General Well-Being Index (with specific domains).

Questionnaires	Pre treatment	After treatment	p-value
Short form 36 ($n=15$)	76.2 ± 3.9	75.4 ± 3.8	0.66
Pain	73.8 ± 6.2	72.8 ± 5.2	0.87
Physical function	92.7 ± 2.2	91.7 ± 2.7	0.49
Physical problem	88.3 ± 8.0	85.0 ± 8.0	0.16
Social activities	72.5 ± 7.1	74.2 ± 6.0	0.74
Mental health	66.8 ± 5.2	65.3 ± 5.9	0.73
Emotional problems	80.0 ± 6.5	81.1 ± 8.4	0.91
Energy	59.0 ± 5.7	60.3 ± 5.1	0.36
General health	65.0 ± 5.3	61.7 ± 5.3	0.51
Green Climacteric Scale ($n=10$)	13.8 ± 2.3	13.8 ± 3.4	0.99
Anxiety	3.6 ± 0.9	3.3 ± 0.9	0.73
Depression	4.4 ± 1.9	3.7 ± 1.1	0.45
Somatic	4.2 ± 0.6	4.3 ± 3.7	0.91
Vasomotor	0.4 ± 0.2	0.7 ± 0.3	0.17
Sexual dysfunction	1.2 ± 0.8	1.3 ± 0.3	0.68
The Psychological General Well-Being Index ($n=15$)	57.3 ± 1.2	58.4 ± 0.9	0.28
Anxiety	14.8 ± 0.8	16.1 ± 3.9	0.1
Depression	10.3 ± 0.2	10.1 ± 0.4	0.36
Well-being	10.3 ± 0.2	10.5 ± 0.4	0.70
Self-control	5.2 ± 0.4	5.4 ± 0.4	0.81
General health	8.3 ± 0.5	8.5 ± 0.3	0.77
Vitality	8.0 ± 0.4	7.9 ± 0.5	0.66

are also components of the hormonal replacement therapy (HT), but perimenopausal premenstrual symptoms (that can be identified as the ones that occur in perimenopause) can be caused by exogenous progesterone [27]. The fruit extract Vitex Agnus Castus is the only phytotherapy which has shown a beneficial action for controlling irritability and mood swings in placebo-controlled trials [28]. Our limited results obtained in premenopausal women do not allow us to state that this preparation can improve mood swings, but more than half of the women in this study experienced a promising amelioration in terms of depression and headache.

The major limitation of this study is the small sample size and the short follow-up (only 3 cycles of treatment): thus, it should be considered a pilot study. Furthermore, it was conducted in a single center, and we did not include a placebo or control group. For all of these reasons, these results should be considered preliminary, although worthy enough to be explored in a larger investigation. We will also need longer follow up periods to evaluate oncologic outcomes, specifically in relation to breast cancer risk: for this reason, this data should be considered with caution.

In conclusion, unfortunately, there is still a lack of data regarding the effect of phyto-progestins and their use in women when compared to synthetic progestins. This also comes from a lack of standardization of the specific products used and the exact quantities contained, which are a widespread fact in phytotherapy treatments in general. In light of our research, we think that a combination of Dioscorea Villosa, Agnus Castus and Damiana could be a promising candidate to treat menstrual irregularities without an organic cause, with a significant reduction of menstrual pain and flow intensity and possible additional benefits in PMS symptoms treatment in women at high risk for breast cancer and breast cancer survivors, who have a contraindication to the use of synthetic progestins.

Disclosure statement

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [GG], upon reasonable request.

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