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Adverse symptoms during short-term use of ulipristal acetate in women with uterine myomas and/or adenomyosis

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Abstract

Aim: To evaluate various adverse symptoms during short-term use of ulipristal acetate in women with uterine myomas (n = 90), adenomyosis (n = 3) or both (n = 7).

Methods: One hundred premenopausal women who received ulipristal acetate for 4–12 weeks during 2016 to 2017 were selected. The medical records were reviewed and the following information was collected; adverse symptoms during medication, presence of menorrhagia or menstrual cramps, blood hemoglobin and liver function test. Adverse symptoms were recorded in the medical records as a checklist form including 76 specific progestin-related symptoms.

Results: Overall, the most frequent adverse symptom was amenorrhea (43%), followed by weight gain (29%), fatigue (27%), abdominal discomfort (21%), decreased menstrual flow (19%) and dizziness (18%). In 89 symptomatic women (with heavy menstrual bleeding and/or menstrual cramping pain and/or anemia), the most frequent adverse symptom was weight gain (27%) and fatigue (27%), followed by abdominal discomfort (21%), dry eye (18%), facial flushing (17%), dizziness (17%), headache (17%) and increased vaginal discharge (15%). Fourteen women stopped the medication due to unwanted adverse symptoms. Of this discontinuation group, major complaint was fatigue (50%), followed by weight gain (36%) and breast discomfort (35.7%).

Conclusion: Adverse symptoms were common and discontinuation rate was somewhat higher during short-term course of ulipristal acetate. Information about incidence of various adverse symptoms should be given to women who willing to take ulipristal acetate.

Key words: adenomyosis, adverse symptom, discontinuation, myoma, ulipristal acetate.

Introduction

Ulipristal acetate has emerged recently as a new treatment option for uterine myomas. It appears to be a good alternative for women who are seeking fertility preservation rather than surgery.[1] Ulipristal acetate is one of selective progesterone receptor modulators (SPRM) and induces shrinkage of uterine myomas acting as a progesterone antagonist.[2,3] The pathophysiology of the progesterone pathway in the uterine myomas has been elucidated, and the efficacy of SPRM has been demonstrated by several randomized controlled trials.[4,5] Alleviation of uterine myoma-related symptoms, such as heavy menstrual bleeding, menstrual cramping pain or pelvic pain was demonstrated.[6–10] However, adverse symptoms were reported in approximately 50% of the women in the PEARL I trial and approximately 80% of the women

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in the PEARL II trial.[9] Various adverse symptoms during ulipristal acetate 5 mg have been reported in PEARL I to IV trials; headache (4–26%), hot flush (6–26%), abdominal pain (2–6%), nausea (2–6%), fatigue (1–4%), breast pain (2–5%) and constipation (0–4%).[9]

In both PEARL I and II trials, the discontinuation rate due to adverse symptoms was reported to be approximately 1%.[8,11] In PEARL IV trial, the discontinuation rate due to adverse symptoms was less than 5%.[12] Specifically, in the first course of ulipristal acetate 5 mg, adverse symptoms leading to dropout occurred in 2.6% of the on-treatment women and in 0.9% of the off-treatment women. In the second course, adverse symptoms leading to dropout occurred in 0.5% of the on-treatment women and in 0% of the off-treatment women.[12]

Amenorrhea may be associated with specific endometrial change occurring after SPRM medication. SPRM associated endometrial change (PAEC) involves features that have an atrophic rather than a hyperplastic character. These include cystic dilatation of glands lined by inactive epithelial cells, compact endometrial stroma without predecidual change and/or abnormal vasculature.[13–15] In PEARL I trial, SPRM-associated endometrial change was noted in 62% and 57% in group of ulipristal acetate 5 mg and 10 mg, respectively, but they were usually resolved 6 months after the end of treatment.[8] SPRM-associated endometrial change was noted in 58% and 59% in group of ulipristal acetate 5 mg and 10 mg, respectively.[12] Rarely, endometrial hyperplasia could be occurred, but the incidence has been reported to be less than 1%.[12]

To minimize the development of PAEC and to encourage the resolution of PAEC, medication-free interval is recommended before the next medication schedule; usually, women experience once menstruation after 12 weeks' course of ulipristal acetate and then the next course of medication starts during the forthcoming menstruation.

Ulipristal acetate acts as a progesterone antagonist on uterine myomas, however, it acts as a progesterone agonist on other tissues, thus various progestin-related adverse symptoms can be emerged.

In PEARL I study, headache (4%) and constipation (4%) were the most common adverse symptoms in ulipristal acetate 5 mg users.[8] In PEARL II and IV studies, headache (26% and 9.1%, respectively) and hot flush (26% and 5.7%, respectively) were the most common adverse symptoms in ulipristal acetate 5 mg users.[11,12]

In a recent report by Simon *et al.*,[16] the most frequent adverse symptoms during use of ulipristal acetate 5 mg was hot flush (5.7%). They reported that none of the women discontinued their medications due to adverse symptoms or events.

In Korea, ulipristal acetate (5 mg) has been launched since July 2012 and is currently being widely used in women with uterine myomas. However, there have been no reports on the incidence of adverse symptoms during use of ulipristal acetate in Korean women. Most clinicians prescribe ulipristal acetate for 4, or 8 or 12 weeks, and then check adverse symptoms or events at the next visit. Checking adverse symptoms or events is clinically important step because clinicians should determine whether the medication continued or discontinued.

In the present study, we investigated incidence of adverse symptoms during use of ulipristal acetate for 4–12 weeks in women with uterine myomas and/or adenomyosis.

Methods

One hundred premenopausal women who received ulipristal acetate for 4–12 weeks during 2016 to 2017 at the Seoul National University of Bundang Hospital were selected. The medical records were retrospectively reviewed and following information were collected: age, body mass index previous medical or surgical history, major diagnosis, type and diameter of uterine myomas, presence of heavy menstrual bleeding or menstrual cramping pain, blood hemoglobin, liver function test, adverse symptoms during medication and duration of medication. The Institutional Review Board of the Seoul National University Bundang Hospital approved the use of medical records (IRB No. B-1805-466-105).

Adverse symptoms were recorded in the medical records as a checklist form including 76 specific progestin-related symptoms. They were categorized as nine items including genitourinary system, metabolic or nutritional system, psychological system, nervous system, eye/ear/mouth system, cardiorespiratory system, gastrointestinal system, dermatologic system and musculoskeletal system.

The mean age of the women was 43.1 $\pm$ 5.5 years (range: 20–50 years) and the mean body mass index was 23.3 $\pm$ 3.5 kg/m^2. The mean number of child was 1.3 $\pm$ 0.9. Before the use of ulipristal acetate, 19 women received various medical treatments such

as GnRH agonist, oral contraceptives or dienogest. Eleven women used levonorgestrel intrauterine system but failed to control her menstruation-related symptoms.

The past surgical treatments were as followings; laparoscopic myomectomy in 9 women, hysteroscopic myomectomy in 6 women, adnexa surgery in 6 women, open myomectomy + adnexa surgery in 5 women, open myomectomy in 2 women and other surgical treatments in 7 women.

The diagnosis was made by ultrasonographic evaluation; uterine myoma in 90 women, uterine adenomyosis in 3 women, and both in 7 women. Among 97 women with uterine myoma, intramural type was noted in 60 women, subserosal type in 22 women, and sub-mucosal type in 8 women (If one woman had multiple uterine myomas, one representative type was assessed). Type of myomas could not be identified in the medical records from 7 women. The mean diameter of (representative) myoma was 5.4 ± 1.9 cm (range: 2–12 cm).

SPSS version 22 (IBM, Armonk, NY, USA) was used for statistical analysis.

Results

Before start of ulipristal acetate, 71 women complained of heavy menstrual bleeding and 44 women complained of menstrual cramping pain. Twenty-eight women complained of both heavy menstrual bleeding and menstrual cramping pain. Menstrual amount was recorded in 11 women as pictorial blood assessment method and the mean score was 209.5 ± 102.2 (range: 109–432). Pre-treatment blood hemoglobin level was recorded in 38 women and the mean blood hemoglobin level was 10.7 ± 2.4 g/dL (range: 5.9–14.5 g/dL). Seventeen women (44.7%) showed blood hemoglobin level less than 10.0 g/dL.

At least one adverse symptom was noted in 97 women (97%). Overall, the most frequent adverse symptom was amenorrhea (43%), followed by weight gain (29%), fatigue (27%), abdominal discomfort (21%), decreased menstrual flow (19%), dizziness (18%), dry eye (17%), headache (16%), increased vaginal discharge (16%), facial flushing (15%), breast discomfort (14%), dry mouth (12%), sleep disturbance (11%), drowsiness (11%), gas distension (11%), alopecia (11%) and febrile sense (10%) (Table 1). Irregular vaginal bleeding was rare event; only two women complained of irregular vaginal bleeding. Other

Table 1 The frequency of adverse symptoms during use of ulipristal acetate for 4–12 weeks in all patients' group

Adverse symptoms	%
<Reproductive system>	
Irregular vaginal bleeding	2
Increased pain	0
Increased menstrual flow	4
Decreased menstrual flow	19
Amenorrhea	43
Breast discomfort	14
Vaginitis	4
Dryness of vagina	7
Increased vaginal discharge	16
Premenstrual syndrome	4
Cystitis	2
<Metabolic or nutritional system>	
Weight gain	29
Appetite increase	6
Edema	10
Weight loss	2
Facial flushing	15
Febrile sense	10
Chills	3
<Psychological system>	
Anxiety	4
Depressive mood	9
Nervousness	8
Sleep disturbance	11
Dizziness	18
Fatigue	27
Drowsiness	11
Decreased libido	6
Increased libido	0
<Nervous system>	
Headache	16
Migraine	5
Asthenia	9
<Eye/ear/mouth system>	
Dry eye	17
Blurred vision	3
Protruding eyes	0
Diplopia	0
Tinnitus	3
Gingivitis	2
<Cardiorespiratory system>	
Increased pulse	2
Hypotension	2
Hypertension	0
Difficult breathing	1
<Gastrointestinal system>	
Decreased appetite	5
Nausea	3
Vomiting	1
Abdominal pain	3
Gas distension	11
Abdominal discomfort	21
Diarrhea	5
Constipation	5

Table 1 Continued

Adverse symptoms	%
Gastritis	4
Enteritis	0
Jaundice	0
Dry mouth	12
<Dermatologic system>	
Acne	9
Alopecia	11
Hirsutism	0
Skin dryness	6
Sweating	4
Itching	9
Urticaria	1
Nail breakage	1
Dandruff increase	3
Dermatitis	4
Rash	0
Photosensitive reaction	0
Pigmentation	0
Erythema multiform	0
<Musculoskeletal system>	
Dorsal pain	9
Bone pain	2
Muscle cramps	0
Limb pain	2
Limb weakness	7

adverse symptoms that were not listed in the checklist were knee pain (1%), a decrease in vaginal discharge (1%), nocturia (1%) and urinary incontinence (1%).

Amenorrhea or decreased menstrual flow might be advantageous in women with heavy menstrual bleeding and/or menstrual cramps and/or anemia. Thus, amenorrhea or decreased menstrual flow would not be a side effect in 89 symptomatic women. In this situation, the most frequent adverse symptom was weight gain (27%) and fatigue (27%), followed by abdominal discomfort (21%), dry eye (18%), facial flushing (17%), dizziness (17%), headache (17%), increased vaginal discharge (15%), breast discomfort (13%), dry mouth (12%), febrile sense (11%), sleep disturbance (11%), drowsiness (11%), gas distension (11%) and alopecia (11%).

Among 71 women with heavy menstrual bleeding, more than half of the women (63.4%) showed improvement in symptoms; decreased menstrual flow was noted in 18 women (25.3%) and amenorrhea was noted in 27 women (38.0%) after taking ulipristal acetate. Among 44 women with menstrual cramping pain, decreased menstrual flow was noted in 8 women (18.2%) and amenorrhea was noted in 19 patients (43.2%).

Among 17 women with blood hemoglobin less than 10 g/dL, amenorrhea or decreased menstrual flow was noted in 11 women (64.7%). Nonetheless, increased menstrual flow was noted in two women.

Fourteen women stopped the medication due to unwanted adverse symptoms. In the discontinuation group, major complaint was fatigue (50%), followed by weight gain (35.7%), breast discomfort (35.7%), dizziness (28.6%), asthenia (28.6%), dry eye (28.6%), gas distension (28.6%), abdominal discomfort (28.6%) and itching (28.6%).

Liver function test was performed in 14 women during medication (3 women) or after the discontinuation of the medication (11 women, interval between the discontinuation and liver function test: 3–12 weeks). In only one woman, aspartate transaminase (AST) and alanine transaminase (ALT) were elevated (52/67 IU/L) at 3 weeks later since the discontinuation of the medication due to multiple adverse symptoms (breast discomfort, asthenia, fatigue, gas distension, abdominal discomfort and itching). However, AST/ALT value was normalized 2 weeks later.

Discussion

In the present study, three common adverse symptoms during short-term course of ulipristal acetate overall were amenorrhea (43%), weight gain (29%) and fatigue (27%). Amenorrhea or decreased menstrual flow could be helpful to women with menorrhagia and/or menstrual cramps and/or anemia, thus those might not be adverse symptoms. In those 89 women, the most frequent adverse symptom was weight gain (27%) and fatigue (27%), followed by abdominal discomfort (21%), dry eye (18%), facial flushing (17%), dizziness (17%), headache (17%) and increased vaginal discharge (15%).

The amenorrhea incidence itself was quite different from study to study. The incidence of amenorrhea was 73% in the PEARL I trial, 75% in the PEARL II trial and 62% in the PEARL IV trial, when 5 mg of ulipristal acetate was used.[8,11,12] In contrast, the incidence of amenorrhea was 47.2% in a recent study by Simon *et al*.,[16] which is similar to our study.

Weight gain (29%) was the second most common adverse symptom in our study, but this was not a major adverse symptom in PEARL I, II and IV trial and a recent study by Simon *et al*.[8,11,12,16] In fact, weight gain was the second most common adverse

symptom in the discontinuation group in our study. We think that the Korean women are more prone to gain her weight during short course of ulipristal acetate.

Fatigue (27%) was the third most common adverse symptom in our study, but this was minor adverse symptom in PEARL II trial (1.3%) and PEARL IV trial (4%).[11,12] In fact, fatigue was the most common adverse symptom in the discontinuation group in our study (50%).

Headache was the most common adverse symptom in PEARL I (4%), PEARL II (26%) and PEARL IV trial (9.1%), but in our study, headache was not a major complaint (16%).[8,11,12]

Hot flush was the major adverse symptom in PEARL II (26%) and PEARL IV trial (5.7%), and a study by Simon *et al*. (5.7%), but in our study, hot flush was not a major complaint (15%).[11,12,16]

Discontinuation rate due to adverse symptoms was approximately 1% in both PEARL I and II trials and less than 5% in PEARL IV trial.[8,11,12] In a study by Simon *et al*.,[16] none of the women discontinued the medication due to adverse symptoms. In the present study, the discontinuation rate was rather high (14%) and frequent adverse symptoms in the discontinuation group were fatigue, weight gain and breast discomfort. Considering fatigue is one of the most important reasons for quitting drugs, careful consideration should be given in deciding whether to maintain the drug if this symptom occurs in patients with ulipristal acetate.

In the present study, serum AST/ALT levels were mildly elevated but normalized 2 weeks later in only one woman (7.1%) among 14 women who performed liver function test during or after ulipristal acetate use. Nieman *et al*.[7] reported that elevation of serum AST and/or ALT levels was observed in 9 women (23%) who received ulipristal acetate for 12 weeks, but the dose was 10 mg or 20 mg. Levens *et al*.[6] reported that transient elevation serum AST and/or ALT level was observed in only one woman (16%) who received ulipristal acetate for 12 weeks, but the dose was 20 mg.

Nausea, vomiting, jaundice, as well as fatigue may be signs of hepatic dysfunction. Considering relatively higher incidence of fatigue (27%) in the present study, liver function test would be a reasonable option in women who complain fatigue. In the present study, the incidence of nausea and vomiting was relatively low (3% and 1%, respectively), and none of the women complained jaundice.

On March 22, 2018, the European Commission (EC) announced the importance of liver function test in women taking ulipristal acetate based on cases of severe liver damage and/or liver failure.[17] The EC recommended that women should be performed liver function tests at least 1 month interval during the course of ulipristal acetate and at 2–4 weeks after the discontinuation. In addition, EC recommended that liver function tests should be performed anytime when there are signs of liver damage, such as nausea, vomiting or jaundice.

Limitation of our study was that the intensity or severity of adverse symptoms was absent in the medical records. A more detailed assessment should further be performed by measuring the severity of the adverse symptoms. Nevertheless, our study has several strengths. Adverse symptoms were recorded in the medical records as a checklist form including 76 specific progestin-related symptoms. Through patient-reported adverse symptoms, the true incidence of adverse symptoms may be underestimated. The primary outcome of the study was a detailed analysis of the side effects as a main focus, which is different from previous papers that have studied the side effect just as an additional aspect of the action.

In conclusion, we here presented the types and incidence of various adverse symptoms during use of ulipristal acetate 5 mg for 4–12 weeks as well as the discontinuation rate due to adverse symptoms in Korean women with uterine myomas and/or adenomyosis. It can be helpful for patient counseling before taking ulipristal acetate. Further investigations should be conducted as to adverse events after long-term use of ulipristal acetate.

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Disclosure

None of the authors has any conflict of interests regarding publication of this paper.

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