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Confirmation of menopause based on changes in follicle-stimulating hormone levels in patients who were administered dienogest

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Summary

Purpose of investigation: The appropriate time for patients to discontinue dienogest (DNG) after long-term use has been a recent topic of debate. Therefore, this study evaluated the timing for discontinuation of DNG in climacteric patients suffering from endometriosis and adenomyosis. *Materials and Methods:* DNG was orally administered at 2 mg/day for more than 12 months. The serum estradiol (E2) and follicle-stimulating hormone (FSH) levels were measured every three to six months. DNG was discontinued when the hormone levels changed to those characteristic of menopause. *Results:* FSH levels in three patients increased to more than 25.8 mIU/mL during DNG administration. They were thus diagnosed as having entered menopause. There was no recurrence of pain in these patients at one year after discontinuation of DNG. *Conclusion:* An increase in serum FSH levels could help in confirming the diagnosis of menopause. In addition, DNG prevented the recurrence of endometriosis and adenomyosis.

Key words: Dienogest; Endometriosis; Adenomyosis; Estradiol; Follicle-stimulating hormone.

Introduction

Gonadotropin-releasing hormone agonists (GnRH agonists) are effective in the treatment of endometriosis and adenomyosis. However, the side effects of these medications include liver dysfunction, ovarian deficiency symptoms with low estrogen levels, and severely decreased bone density. Furthermore, their use has been limited to six months because a hypoestrogenic state leads to a reduction in bone mineral density in Japanese women.

A combination of low-dose estrogen and progestin (LEP) has been commonly used as an oral contraceptive. In later years, LEP has been prescribed as an inexpensive drug for the treatment of endometriosis when painkillers and Japanese herbal medicines are ineffective. However, LEP is inferior to GnRH agonists and dienogest (DNG) with respect to efficacy, and the side effects of chronic LEP administration include irregular bleeding, thrombosis, and liver dysfunction.

DNG is a fourth-generation progestin that is widely used in the long-term treatment of endometriosis and adenomyosis because of its efficacy and safety. DNG is an agonist to the human progesterone receptor (PR), and it does not have agonist activity against androgen, glucocorticoid, or mineralocorticoid receptors [1]. There are only a few side effects, such as irregular bleeding. Thus, DNG can be used to treat the symptoms of endometriosis (dysmenorrhea or pelvic pain) and can improve the long-term quality of life of women. However, there is uncertainty regarding the use of DNG in patients in their 40s and 50s. Therefore, the following study evaluated the effects of long-term DNG administration with a particular focus on perimenopausal-aged women.

Materials and Methods

The study participants were three women aged approximately 50 years who had visited the Kanazawa Medical University Hospital, Department of Obstetrics and Gynecology. These three patients were treated from May 2008 to July 2014. Informed consent was obtained from all participants in the study.

DNG was administered as a 2 mg/day oral dose for more than 12 months. The serum E2 and FSH levels were measured every three to six months. The serum estradiol (E2) and follicle-stimulating hormone (FSH) levels were measured using a electrochemical luminescence immunoassay. According to the present hospital laboratory, the normal ovarian function reference values were 1.7–12.4 mIU/mL for FSH and 24.5–261 pg/mL for E2; the postmenopausal reference values were >25.8–134.8 mIU/mL for FSH and <39.5 pg/mL for E2. DNG was discontinued after confirmation that the serum FSH levels were at postmenopausal reference values. After discontinuation of DNG, the subjective symptoms (dysmenorrhea or pelvic pain) were recorded over 12–18 months, and the serum E2, FSH, and tumor marker levels were assessed. A follow up was conducted to assess symptom recurrence.

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Results

The three patients had serum E2 and FSH levels that were indicative of sexual maturity prior to menopause. The description of each case is as follows.

Case 1

A 52-year-old Japanese woman (gravida 1, para 1) visited the present department for dysmenorrhea. At that time, her height and weight were 157 cm and 56 kg, respectively, with a BMI of 22.7 kg/m^2. She had a medical history of hyperthyroidism and had undergone laparoscopic ovarian cystectomy for a left endometrioma. She did not have any additional medical or family history of relevance. At this hospital, she was administered both LEP and Japanese herbal medicines for dysmenorrhea, but her symptoms did not improve. Therefore, the treatment was changed to DNG. Her pretreatment laboratory test results, including a complete blood count, serum biochemical analysis, and urine analysis, were normal. Her pretreatment cancer antigen 125 (CA-125) level was 63.0 U/mL (normal range, <35 U/mL). She was diagnosed with stage III endometriosis based on the Revised American Society for Reproductive Medicine (r-ASRM) classification. The patient took DNG for over 12 months to treat endometriosis and DNG was discontinued when her hormone levels became characteristic of those during menopause. She was followed up for 18 months after discontinuing DNG, with no resumption of menses or recurrence of pelvic pain.

Case 2

A 53-year-old Japanese woman (gravida 3, para 2) visited the present department for hypermenorrhea and dysmenorrhea. At the time, her height and weight were 148 cm and 76 kg, respectively, with BMI of 29.2 kg/m^2. She did not have a medical or family history of any relevance. She was severely anemic because of hypermenorrhea. Anemia was treated with a leuprorelin 1.88 mg for six months. Her treatment was subsequently changed to DNG. Her pretreatment laboratory test results demonstrated anemia with hemoglobin levels of 7.2 g/dL. Her other laboratory test findings, including her CA12-5 levels, were within the normal reference ranges. Her clinical diagnosis was adenomyosis and fibroid tissue. She took DNG for 34 months to treat adenomyosis and fibroid tissue, and discontinued it when her hormone levels became characteristic of those during menopause. She was followed up for 12 months after discontinuing DNG, with no resumption of menses or recurrence of pelvic pain. There was a 32.6% reduction in adenomyosis (bidirectional measurement) between the discontinuation of DNG and the imaging that was performed one year later, as shown by MRI (Figure 1).

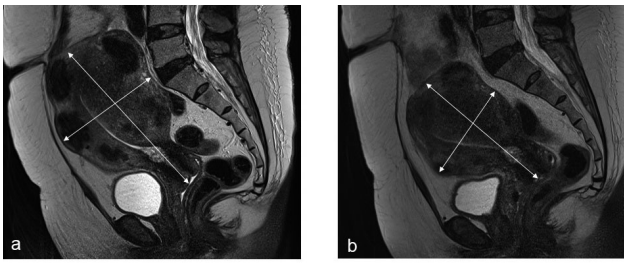

Figure 1. — a) Dienogest discontinuation time uterus size 162.4×101.4 mm. b) One year later uterus size 126.4×83.1 mm, 32.6% reduction (bidirectional measurement)

Case 3

A 49-year-old Japanese woman (gravida 3, para 3) visited the present department for right-sided abdominal distension. At the time, her height and weight were 161 cm and 53 kg, respectively, with BMI of 20.4 kg/m^2. She did not have a medical or family history of any relevance. Ovarian enlargement was discovered on CT during her hospital stay in the Internal Medicine Department, and she was diagnosed with endometriosis by ultrasonography and MRI. She was treated with DNG for six months and subsequently underwent right oophorectomy. DNG was again administered after the surgery to prevent recurrence. Her pretreatment laboratory test results showed mild anemia (hemoglobin level of 9.9 g/dL) and slightly elevated AST (51 U/L) and ALT (31 U/L) levels. Her pretreatment CA-125 level was 176.7 U/mL (normal range, <35 U/mL). Her clinical diagnosis was stage III endometriosis based on the r-ASRM classification. She took DNG for 19 months for endometriosis and discontinued it when her hormone levels became characteristic of those during menopause. She was followed up for 12 months after discontinuing DNG, with no resumption of menses or recurrence of pelvic pain.

Changes in FSH levels over time in these three patients are shown in Table 1. Three patients had changed increase of FSH levels during treatment with DNG. FSH levels increased further even after discontinuation of treatment with DNG, and there was no resumption of menses or recurrence of pelvic pain in any patient.

Discussion

Therapeutic drugs used to treat endometriosis have different mechanisms of action (Table 2). GnRH agonists can induce a flare-up phenomenon with temporary secretion of large quantities of gonadotropin from the pituitary gland. GnRH receptors cause downregulation when administered continuously. The secretion of luteinizing hormone (LH) and FSH from the pituitary gland is inhibited, which decreases ovarian hormone levels (E2 and P4). Therefore, LH, FSH, and E2 levels are typically low with GnRH ago-

Table 1. — *Change over time of FSH level before and after the discontinuation of dienogest administration.*

Case	Pre (month)	-12	-6	0	6	12	18
1	12.9	10.8	25.2	50.4	23.6	50.1	73.9
2	5.6	17.4	29.2	27.2	59.4	65.4	-
3	13.7	5.8	26.8	30.6	46.3	78.8	-
FSH mean (mIU/mL)	10.7	11.3	27.1	36.1	43.1	64.8	73.9
Administration		Dienogest 2 mg/day		Discontinuation	Follow up		
Clinical course		No recurrence of pelvic pain No irregular bleeding			No recurrence of pelvic pain No resumption of menses		

Table 2. — *Change of main blood hormone concentrations with dysmenorrhea therapeutic drug.*

Drug for endometriosis	ovulation	LH surge	FSH	LH	E2
GnRH agonist	Inhibition	Inhibition	↓	↓	↓↓
LEP	Inhibition	Inhibition	↓	↓	↓↓
DNG	Inhibition	Inhibition	→	→	↓

GnRH agonist: gonadotropin-releasing hormone agonists; LEP: low-dose estrogen and progestin; DNG: dienogest.

nist administration. Even if menopausal patients are administered artificial hormones, their hormone levels do not change [2, 3].

LEP acts on the hypothalamus and pituitary gland and inhibits ovulation and LH surge. Serum FSH levels are low during LEP administration and cannot predict menopause during the dosing period. Serum FSH levels approach menopausal levels two weeks after discontinuation of LEP [4, 5]. It is necessary to measure E2 and FSH levels several weeks after LEP termination to diagnose menopause [6].

In contrast, DNG has been studied for its effect on ovarian function. Sasagawa *et al.* [7] studied two groups of female cynomolgus monkeys, one was the control group and the other group was administered a single oral dose of 0.1 mg/kg DNG on day 7 of the menstrual cycle. This research team determined that DNG inhibited the LH surge and ovulation through stimulation of the hypothalamo-hypophyseal system, but the reduction in plasma E2 levels was not channeled through FSH secreted by the pituitary gland; they also found that DNG inhibited initial dominant follicle atresia and estrogen increase of the follicular phase, but DNG did not affect the ovarian follicle prior to it becoming a dominant follicle. Therefore, DNG has a strong effect on the ovaries. [8] However, it may be difficult to show a hormonal inhibitory action for the hypothalamus/pituitary gland, unlike the effect observed with GnRH agonists [9]. Based on these mechanisms, a diagnosis of menopause is possible using serum FSH levels when a patient is taking DNG.

Menopause (as defined by the World Health Organization) is the permanent cessation of menstruation due to a loss of ovarian follicular activity [10]. Medical professionals often define menopause as having occurred when a woman has not had any vaginal bleeding for a year [11]. It may also be defined by a decrease in hormone production by the ovaries [12]. The present authors reviewed various articles that described the average age of menopause in Japanese women. Kono *et al.* [13] reported that the crude mean age of menopause was 49.33 years in postmenopausal participants over 40 years. Using the Kaplan–Meier life table analytical method, Yasui *et al.* [14] reported that the median age at menopause was 52.1 years. Based on these reports, the menopausal period of Japanese women is 45–56 years. For women in this age category, it is important to determine the appropriate time for discontinuation of DNG for endometriosis and adenomyosis.

Finally, Fagervold *et al.* [15] reported that the symptoms of endometriosis (pelvic pain) disappeared in 96.9% of women after menopause. In addition, it is believed that most symptoms of adenomyosis are reduced at menopause, and treatment is not necessary except in some extreme cases.

Conclusion

The three patients in menopausal transition in this present report displayed increases in FSH levels to menopausal ranges during DNG administration. The menopausal transition was associated with an increase in FSH levels. In particular, the increase in serum FSH levels could help in diagnosing menopause. In addition, when used in this manner, DNG is an effective drug for treating endometriosis and adenomyosis in menopausal women. A future study on the hormonal dynamics of early menopausal women will be necessary to eliminate the challenges in determining when to discontinue DNG.

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