Japan Society of Obstetrics and Gynecology and Japan Society for Menopause and Women’s Health 2017 guidelines for hormone replacement therapy*

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Abstract

Hormone replacement therapy (HRT) plays a large part in maintaining and improving the quality of life (QOL) of postmenopausal women. Despite this obvious role, the use of HRT has stagnated in Japan as well as the United States, since the interim report of the HRT trial of Women’s Health Initiative study was published in 2002. The Japan Society of Obstetrics and Gynecology and Japan Society for Menopause and Women’s Health formulated the Guidelines for Hormone Replacement Therapy in 2009, which was subsequently revised in 2012, with the aim of organizing perceptions about HRT and allowing people to provide or receive HRT with a sense of security. Later on, in light of changes in indications for HRT and attitudes toward its impact on cancer risks, amendments were made again in 2017. With the establishment of the 2017 guidelines, practitioners in Japan are able to address various issues related to HRT with more appropriate judgment. Moreover, the practice of reliable, safe and effective HRT is expected to promote further efforts toward improvement or maintenance of QOL in patients.

Key words: contraindication, guideline, hormone replacement therapy, indication.

Introduction

Postmenopausal hormone therapy, usually called hormone replacement therapy (HRT) in Japan, collectively refers to treatments in which estrogen formulations are administered, and was conceived with the aim of preventing or treating various symptoms and disorders associated with estrogen deficiency. Other than maintaining female reproductive function, estrogen has many physiological functions, and functional disorders due to symptoms related to estrogen loss or estrogen deficiency are inevitable in women with decreased ovarian function (e.g., postmenopausal women), albeit to a varying degree. From these perspectives, HRT

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indisputably offers a convenient and effective means of health care for postmenopausal women.

From time to time, HRT has been suggested to cause unacceptable adverse events. Initially, a rapid increase in the incidence of endometrial cancer was pointed out as a major issue; however, this was found to be attributable to estrogen monotherapy. Moreover, further studies demonstrated that the cancer risk could be suppressed by concomitant progestogen administration, and this regimen, that is, estrogen and progestogen (estrogen progestogen therapy [EPT]), came to be established for use in women with a uterus. Similarly, the 2002 interim report of the HRT trial of Women’s Health Initiative (WHI) study emphasized the risks of HRT, but subsequent verification studies have contested the validity of these risks. As such, assessments of HRT have characteristically evolved and developed, swaying between evaluation of benefits and risks on a continuous basis.

Even today, this dialectical sublation concerning HRT is at the base of continued discussions regarding the choice of appropriate candidates and regimens, making steady progress toward the establishment of evidence-based goals in consideration of certain advantages as well as feared disadvantages. Keeping track of these scientific facts surrounding HRT, which are updated from day to day, is not easy. Therefore, the Japan Society of Obstetrics and Gynecology (JSOG) and Japan Menopause Society (present Japan Society for Menopause and Women’s Health [JMWH]) published guidelines for HRT in 2009, with the aim of organizing perceptions about HRT and allowing people to provide or receive HRT with a sense of security. Later on, this project was passed on to the Women’s Health Care Committee of the JSOG as a joint project with JMWH, leading to the publication of a revised edition in 2012, followed by the release of the current (2017), third revised edition. Thus, the original aim, ‘toward the safe practice of HRT for healthcare providers and recipients,’ has been handed down continually.

There are mainly two ways to increase the benefits of HRT while reducing the risks: to appropriately assess (i) age/years since menopause and (ii) health condition/predisposition/underlying disease of patients; and to select dose regimens tailored to individual patients, including (i) type of drugs, (ii) route of administration, (iii) dose, (iv) mode of administration and (v) duration of administration. The part of ‘Clinical Questions (CQ) and Answers’, a newly established component of the revised 2017 edition, aims to provide specific answers to these questions based on currently available evidence. Recognizing the fact that the benefit–risk profile varies according to differences in patient age and health condition, these CQs were developed, once again in light of the original aim, on the basis that appropriate patient assessment and dose regimen selection are important.

The scope of indications for HRT is expanding, as the postmenopausal generation continues to stay socially active. On the other hand, HRT is a rare modality in that no other therapies have been so repeatedly verified, in terms of their merits and demerits, and continuously evolved worldwide. What this means is that there are no alternatives or substitutes for HRT.

This report summarizes the outline of the 2017 guidelines for HRT. Only the headlines are presented here, although both the General Statement section and List of Clinical Questions and Answers section are accompanied with commentary.

Methods

These guidelines were drafted for physicians who intend to prescribe HRT in Japan. A subcommittee for revising the Japanese guidelines for HRT was established within the Women’s Health Care Committee of the JSOG, and a core committee for developing HRT guidelines was organized in collaboration with JMWH. As for the revision policy, general items relating to HRT were organized as ‘General Statement’, which mainly included the contents of the 2012 version, and additions and amendments were made by adopting new evidence since publication of the 2012 version.

The Committee extracted specific questions regarding the practice of HRT from results of the ‘Survey in Preparation for HRT Guideline Revision’, which was conducted among Board Certified Women’s Healthcare Specialists of JMWH, organized these questions into CQs, and created a new section titled ‘List of Clinical Questions’ comprising items selected/adopted after discussions. Based on each item, the Committee members in charge of drafting conducted a selective and careful literature review of articles currently recognized as evidence, and created a draft text along with contents that should be described as guidelines. Based on opinions submitted by the Evaluation Committee on this draft text, discussions were carried out, and items and their contents that gained supporting votes from two thirds of all members were included in the guidelines. Public comments were requested, and after two public consensus meetings followed by further modifications, the present revised edition was finally completed.
As for the strength of recommendations, the concept of the GRADE (Grades of Recommendations, Assessment, Development and Evaluation) approach was applied. The quality of evidence was rated as high, moderate, low or very low, which are denoted with (+ + + +), (+ + + –), (+ + – –) and (+ – – –), respectively. In terms of the strength of the recommendation, strong recommendations use the phrase ‘we recommend’ or ‘we recommend against’ and the number 1, and weak recommendations use the phrase ‘we suggest’ or ‘we suggest against’ and the number 2.

Furthermore, as a supplementary note, ‘the usefulness of HRT for menopausal women under the following conditions’ is included, and as Appendices, points to note about insured health services related to menopausal disorder and HRT are provided in addition to the conventional HRT questionnaire form.

In recent years, ‘hormone therapy (HT)’ or ‘menopausal hormone therapy (MHT)’ has been proposed as an alternative term for ‘HRT’ in Europe and the United States, and treatment in which estrogen and progestogen are concomitantly administered is referred to as estrogen/progestogen therapy (EPT), while estrogen monotherapy is referred to as estrogen therapy (ET). In contrast, in Japan, the distinction between HRT and ERT is not necessarily strict, and HRT is considered to encompass both EPT and ET (i.e., HRT = EPT + ET). Accordingly, in this report, both the terms ET and EPT are used, and when referring to HRT as a whole, taking into consideration the Japanese convention that HRT = HT.

Characteristics of HRT and General Precautions for Use

- HRT has two aspects: it can be used to alleviate symptoms caused by estrogen deficiency or treat disorders, or it is prescribed to asymptomatic postmenopausal women for the purpose of reducing risks for various diseases associated with estrogen deficiency or for healthcare purposes. When initiating HRT, the proper purpose(s) should be considered first.
- HRT, when used properly, is beneficial for promoting or maintaining quality of life (QOL) in postmenopausal women, but might cause harmful effects at times. The benefits and risks of HRT should be carefully considered before use.
- When HRT is initiated for the purpose of reducing risks for various diseases associated with estrogen deficiency or for healthcare purposes, guidance should be provided concurrently regarding the promotion of appropriate lifestyle habits (e.g., diet, smoking, alcohol intake, exercise and so on).
- When planning HRT, risk assessment should be performed prior to administration, and if risks are considered to be high, therapies other than HRT should be considered. Prior to administration, the presence of complications or existing medical conditions should be checked, and breast examination using a diagnostic imaging method should be performed. After initiation of administration, examinations should be performed at least once a year to evaluate benefits and risks.
- In Japan, several different estrogen formulations are currently available, and their routes of administration differ. These formulations are not identical in terms of accompanying benefits and risks.
- Responses to hormonal agents vary by individual, and there are many cases in which effects are observed at doses lower than standard dose. From the standpoint of preventing the onset of adverse drug reactions, starting HRT with small doses are desirable.
- If treatment is intended for atrophic vaginitis only, topical therapy with vaginal estrogen preparations is preferred.
- The purpose of progestogen administration is to prevent endometrial hyperplasia and the increased risk of endometrial cancer during systemic estrogen administration. Therefore, it is not required for women without a uterus or for those receiving lower doses of vaginal estrogen.
- In order to prevent the increased risk of endometrial cancer, combined estrogen and progestogen use is necessary in women with a uterus.
- The treatment period varies by purpose. It is advisable to determine whether to continue treatment or not by assessing the effects and risks of HRT for individual patients. Breast cancer risk has been reported to increase after ≥5 years of EPT in the WHI report. When long-term use is needed, informed consent should be obtained for each case, and judgments should be made accordingly.

General statement

Expected effects of HRT

Menopausal disorders
1. Oral or transdermal estrogen provides relief for hot flashes.
2. Conjugated equine estrogen (CEE) provides relief for night sweats, sexual dysfunction, insomnia, vaginal

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dryness, memory loss, frequent urination and psychological symptoms, in addition to hot flashes.
3. CEE + medroxyprogesterone acetate (MPA) improves health-related QOL.
4. Estradiol (E2) improves sleep disorder, joint pain and limb pain, in addition to hot flashes.

Motor system (bone, cartilage and connective tissue)
1. HRT inhibits bone resorption and increases bone mineral density regardless of differences in formulation or dose.
2. HRT with CEE prevents fractures in both vertebral and nonvertebral bones.
3. Oral and transdermal E2 formulations reportedly have fracture prevention effects similar to CEE.
4. HRT prevents fractures also in healthy women and those with osteopenia.
5. After HRT discontinuation, fracture risk increases relative to during treatment; therefore, those at high risk of fractures require fracture prevention with other agents for treatment of osteoporosis.
6. Estriol (E3) and tissue-selective estrogen complex increase bone mineral density; however, at the moment, there is no evidence for fracture prevention.
7. HRT has a joint protective effect and motor function and posture/balance improving effects.

Lipid metabolism
1. Oral CEE + MPA reduces low-density lipoprotein cholesterol (LDL-C), lipoprotein (a) and remnants, and increases high-density lipoprotein cholesterol (HDL-C).
2. Oral E2 lowers LDL-C.
3. Oral E2 and transdermal E2 do not increase triglycerides (TG).
4. Transdermal E2 exerts antioxidant effects.
5. Transdermal E2 produces larger LDL particles that are resistant to oxidation.
6. Transdermal E2 has an inhibitory effect against vascular inflammation.

Glucose metabolism
1. Oral HRT reduces blood glucose and insulin, and improves insulin resistance.
2. Oral HRT prevents new onset of diabetes mellitus.
3. HRT for the purpose of treating or preventing diabetes mellitus is not recommended.

Cardiovascular system
1. Vascular structures
   a. HRT improves the vascular endothelial function of the brachial artery.
   b. ET starting at early postmenopause suppresses the thickening of the intima-media complex of the carotid artery.
   c. ET does not, at minimum, worsen the elasticity (i.e., stiffness) of the aorta.
2. Blood pressure: HRT does not modulate blood pressure.

Central nervous system
1. Cognitive function
   a. HRT does not improve cognitive function.
   b. HRT may reduce the risk of Alzheimer’s disease.
   c. HRT mainly prescribed for maintaining cognitive function or preventing dementia is not recommended.
2. Mood disorders
   a. HRT improves depressed mood or depressive symptoms during the menopausal transition.
   b. There is no consensus on the effect of HRT on menopausal depression.

Skin
1. There is a possibility that the amount of collagen in skin increases, thereby increasing skin thickness.
2. In skin, HRT has the effect of improving the fineness of the surface layer and viscoelasticity of connective tissue.
3. There is insufficient data to recommend HRT only for the purpose of achieving skin tissue improvement.

Urinary system
1. Oral estrogen administration does not reduce urinary incontinence in postmenopausal women.
2. For the prevention of recurrent urinary tract infections in postmenopausal women, vaginal estrogen administration is effective.
3. For genitourinary syndrome of menopause exhibiting multiple symptoms, vaginal estrogen administration shows superior therapeutic effects compared to other therapies.

Reproductive system
HRT is effective for genital atrophy and related dyspareunia.

Malignant tumors (malignant neoplasms)
1. EPT reduces the risk of colon cancer.
2. HRT may reduce the risk of gastric cancer.
3. HRT reduces the risk of adenocarcinoma of esophagus.

Dental/Oral system
1. HRT increases bone mineral density of the jaw.
2. HRT may improve xerostomia.
3. HRT may prevent tooth loss, and may prevent or improve periodontal disease and other oral symptoms.

Expected adverse events of HRT

Genital bleeding
HRT may cause genital bleeding when administered to women with a uterus.

Breast pain
1. According to package inserts, the frequency of breast pain due to estrogen formulations used in Japan is often less than 10%.
2. Reducing the amount of estrogen is considered effective for alleviating breast pain.

Migraine
HRT may exacerbate pain, but is not necessarily contraindicated.

Breast cancer
1. The risk of breast cancer attributable to HRT is rare.
2. The increased risk of breast cancer seems to be associated with the use of progestogen with estrogen therapy in women with a uterus, and may be related to the duration of use.
3. The risk may decrease after treatment is stopped.

EPT
- Although the risk of invasive breast cancer increases with prolonged duration of use, no significant increase is observed for up to 5 years.
- The increase in risk after ≥5 years of use is equal to or less than the increase in risk associated with lifestyle-related factors.
- The risks differ depending on regimens used, and in particular, on the type of progestogen used.

ET
- Although the risk of invasive breast cancer increases with prolonged duration of use, no significant increase is observed for at least up to 7 years.
- Even after ≥7 years of use, it is considered to take ≥10 years before a significant increase in risk is observed.

Moreover, the risk increase is equal to or less than the risk increase associated with lifestyle-related factors.

Arteriosclerosis/Coronary heart disease
1. Effects of oral HRT on arteriosclerosis
   a. Promotes the development of arteriosclerosis in women with abnormal glucose metabolism.
   b. Increases TG level and reduces the size of LDL particles.
   c. Has a stimulatory effect on vascular inflammation.
   d. MPA lowers HDL-C level and suppresses vascular endothelial function.
   e. Dydrogesterone does not lower HDL-C level or suppress vascular endothelial function.
2. Effects of oral HRT on coronary heart disease.
   a. The risk of developing myocardial infarction due to oral HRT for healthy women increases with age.
   b. Oral EPT increases the risk of developing myocardial infarction in elderly healthy women and women with ischemic heart disease.
   c. Oral HRT should not be used for secondary prevention of coronary heart disease.
   d. Oral HRT does not increase the risk of developing myocardial infarction in healthy women under 60 years of age or within 10 years after menopause at the time of HRT initiation.

Stroke
1. HRT increases the risk of ischemic stroke, but does not increase the risk of hemorrhagic stroke.
2. HRT initiated early after menopause is associated with a low absolute risk of ischemic stroke.
3. Low-dose oral HRT and transdermal HRT may not increase the risk of ischemic stroke.
4. HRT increases stroke risk in hypertensive patients.
5. The discontinuation of HRT negates the increased risk of stroke.
6. HRT has no secondary preventive effect on cerebrovascular disease.

Venous thromboembolism
1. Oral HRT causes a two- to threefold increase in the risk of venous thromboembolism (VTE); the risk is the highest during the first year of administration.
2. The risk of VTE associated with oral HRT increases with increasing age and BMI; however, the absolute risk is low for those who are in their 50s or with a BMI <25 kg/m².
3. HRT increases recurrence risk in those with a history of VTE.
4. HRT with transdermal estrogen may not increase VTE risk.

**Endometrial cancer**
1. For women with a uterus, ET increases the risk of endometrial cancer, whereas EPT does not.
2. In EPT, cyclic regimens pose a higher risk of developing endometrial cancer compared to continuous regimens.
3. The risks differ by the type and dose of estrogen formulation used, the type and dose of progestogen formulation used and regimens.

**Ovarian cancer**
1. The risk of ovarian cancer may increase.
2. The longer the duration, the higher the risk of ovarian cancer.
3. With respect to differences in ovarian cancer risk by regimen, a consensus has not yet been reached.
4. The risk is different in each histological type of ovarian cancer.

**Other tumors**
1. The risk of cervical squamous cell carcinoma does not change, but the risk of cervical adenocarcinoma may increase with ≥5 years of use.
2. HRT is contraindicated for low-grade endometrial stromal sarcoma.
3. The risk of meningioma may increase.
4. Although the risk of malignant melanoma, which has been suggested, may not increase, the risk of basal cell cancer may increase.
5. The risk of lung cancer may decrease.
6. There is a possibility that the size of uterine fibroids may increase, but not to the extent that clinical symptoms may develop.
7. There is a possibility of relapse of endometriosis, but the risk is low.

**Decision-making and management about HRT**

**Contraindicated cases and cases requiring careful administration of HRT**
See Table 1.

**Types and characteristics of drugs**
Hormone formulations used in HRT include estrogens, progestogen and estrogen/progestogen combinations. These are also classified by route of administration as oral, transdermal and vaginal.
Management methods before, during and after HRT

1. Before HRT, measurements of blood pressure, height and body weight, tests for blood count, blood biochemistry and blood glucose, and screening for gynecological and breast cancers are required.
2. During HRT, medical inquiries regarding symptoms should be conducted every patient’s visit, and preadministration examinations above should be repeated once or twice a year.
3. After HRT, gynecological and breast cancer screening is recommended every 1–2 years up to 5 years.

Indications and management algorithms

See Figures 1 and 2.

Clinical Questions and Answers

Symptom/Disease

CQ101: Is HRT effective for joint pain?
Answer: HRT may prevent joint pain.
Level of Recommendation: 2
Level of Evidence (+ + − −)

CQ102: Is HRT effective for insomnia?
Answer: Effective.
Level of Recommendation: 2
Level of Evidence (+ + −)

CQ103: Is HRT effective for back pain?

Indication and stating hormone replacement therapy.

Figure 1 Algorithms for indication and stating hormone replacement therapy.
Answer: If organic disease is ruled out, HRT is effective for back pain which is considered a symptom of menopausal disorder.
Level of Recommendation: 2
Level of Evidence (+ − −)

CQ104: Is HRT effective for pelvic organ prolapsed (POP)?
Answer: HRT does not have a direct effect on pelvic organ prolapse, but improves associated lower urinary tract symptoms, vaginal atrophy and dryness.
Level of Recommendation: 2
Level of Evidence (+ + −)

CQ105: Is HRT effective for glossodynia?
Answer: Some reports suggest it is effective, but sufficient evidence is lacking to actively recommend its use.
Level of Recommendation: 2
Level of Evidence: (+ − −)

CQ106: Does HRT improve sexual dysfunction?
Answer: It improves dyspareunia and vaginal lubrication.
Level of Recommendation: 1
Level of Evidence (+ + −)

CQ107: Is HRT effective for coronary vasospasm and microvascular angina?
CQ108: In surgical treatment of pelvic organ prolapse (POP), is estrogen administration recommended before or after operation?
Answer: In patients with marked vaginal atrophy or inflammation, estrogen administration before and after surgery is recommended, after excluding endometrial atypia.
Level of Recommendation: 2
Level of Evidence (+ − −)

CQ109: Is HRT effective for overactive bladder (OAB)?
Answer: Topical administration of estrogen is effective.
Level of Recommendation: 2
Level of Evidence (+ + −)

Pathological condition/medical history

CQ201: Is HRT possible for smokers?
Answer: It is possible. However, there is a possibility that the beneficial effects may be attenuated, with an increase in adverse events; therefore, guidance should be provided concurrently regarding appropriate lifestyle habits, including smoking cessation.
Level of Recommendation: 2
Level of Evidence (+ + −)

CQ202: Is HRT possible for obese individuals?
Answer: It is possible, although careful administration or conditional administration is required.
Level of Recommendation: 2
Level of Evidence (+ + −)

CQ203: Is HRT possible for women with a history of endometriosis?
Answer: It is possible, but attention needs to be paid to relapse of clinical symptoms, exacerbation or malignant transformation of the lesions.
Level of Recommendation: 1
Level of Evidence (+ − −)

CQ204: Is HRT possible for hypertensive women?
Answer: HRT is possible for women with controlled high blood pressure.

CQ205: Is HRT possible for women with diabetes mellitus?
Answer: It is possible with satisfactorily controlled blood glucose and no arteriosclerotic disease.
Level of Recommendation: 2
Level of Evidence (+ − −)

CQ206: Is HRT recommended for women with premature ovarian insufficiency (POI)?
Answer: Recommended.
Level of Recommendation: 1
Level of Evidence (+ − −)

CQ207: Is HRT recommended for cervical cancer survivors?
Answer: Recommended.
Level of Recommendation: 1
Level of Evidence (+ − −)

CQ208: Is HRT recommended for endometrial cancer survivors?
Answer: Recommended.
Level of Recommendation: 1
Level of Evidence (+ − −)

CQ209: Is HRT recommended for ovarian cancer survivors?
Answer: Recommended.
Level of Recommendation: 1
Level of Evidence (+ − −)

CQ210: Is HRT possible for women with BRCA1/2 gene mutation?
Answer: It is possible for a short term.
Level of Recommendation: 1
Level of Evidence (+ + −)

CQ211: Is HRT recommended for women with no estrogen deficiency symptoms?
Answer: It is recommended if there is a clear goal(s), with benefits outweighing risks.
Level of Recommendation: 1
Level of Evidence (+ − −)

Drugs

CQ301: Is it possible to use oral estriol monotherapy in women with a uterus?

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Answer: It is possible, but attention should be paid to endometrial hyperplasia and genital bleeding. In principle, concomitant progestogen use should be considered for long-term administration.
Level of Recommendation: 1
Level of Evidence (+ + − −)

CQ302: Is it possible to use the levonorgestrel-releasing intrauterine system (LNG-IUS) instead of progestogen in EPT?
Answer: It is possible, but not covered by health insurance in Japan.
Level of Recommendation: 2
Level of Evidence (+ + − −)

CQ303: Is it possible to use selective estrogen receptor modulators (SERM) to achieve endometrial protection in HRT?
Answer: Bazedoxifene is reported to have an endometrium protective effect when used in combination with conjugated estrogen, and may potentially replace progestogens.
Level of Recommendation: 2
Level of Evidence (+ + − −)

**Initiation/Discontinuation**

CQ401: Should the timing of initiation of HRT be taken into consideration in order to reduce cardiovascular adverse events?
Answer: Yes.
Level of Recommendation: 1
Level of Evidence (+ + − −)

CQ402: Is it possible to newly initiate HRT in women beyond age 60?
Answer: It is possible if there is a clear indication, and if its benefits outweigh the risks.
Level of Recommendation: 2
Level of Evidence (+ + − −)

CQ403: How long can HRT be continued?
Answer: There is no set age or administration period that restricts continuation of HRT.
Level of Recommendation: 1
Level of Evidence (+ − − −)

CQ404: Is tapering recommended at the time of HRT termination?

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**Table 2 Usefulness of hormone replacement therapy in menopausal women under various conditions†**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Usefulness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor symptoms</td>
<td>A+</td>
</tr>
<tr>
<td>Depressive symptoms in a climacteric period</td>
<td>A</td>
</tr>
<tr>
<td>Other menopausal disorders</td>
<td>B</td>
</tr>
<tr>
<td>Prevention of Alzheimer’s disease</td>
<td>B</td>
</tr>
<tr>
<td>Treatment of urinary incontinence</td>
<td>C</td>
</tr>
<tr>
<td>Treatment of atrophic vaginitis/dyspareunia</td>
<td>A+</td>
</tr>
<tr>
<td>Prevention of osteoporosis</td>
<td>A+</td>
</tr>
<tr>
<td>Treatment of osteoporosis</td>
<td>A+</td>
</tr>
<tr>
<td>Treatment of dyslipidemia</td>
<td>A</td>
</tr>
<tr>
<td>Prevention of arteriosclerosis</td>
<td>B</td>
</tr>
<tr>
<td>Prevention of skin atrophy</td>
<td>A</td>
</tr>
<tr>
<td>Oral discomfort</td>
<td>B</td>
</tr>
</tbody>
</table>

†, extremely useful; A, highly useful; B, useful; C, there is little evidence for usefulness; D, not useful. and †Needless to say, these evaluations of usefulness may change depending on various conditions, including subject background factors.

Answer: There is no clear basis for recommending tapering over interruption.
Level of Recommendation: 2
Level of Evidence (+ + − −)

CQ405: Should HRT be discontinued during the perioperative period?
Answer: Depending on operative risks, HRT should be discontinued from 4–6 weeks preoperatively up to 2 weeks postoperatively, or until recovery of full ambulation is achieved.
Level of Recommendation: 2
Level of Evidence (+ − − −)

**Others**

CQ501: What should we do when abnormal vaginal bleeding occurs during HRT?
Answer: Possible cause with organic disease should be searched.
Level of Recommendation: 1
Level of Evidence (+ + − −)

CQ502: Can placenta therapy, administration of placenta extracts, be a substitute to HRT for menopausal disorder?
Answer: It will not substitute HRT.
Level of Recommendation: 1
Level of Evidence (+ − − −)

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Supplementary Notes

Table 2 shows the usefulness of HRT in menopausal women under various conditions (usefulness in this context is different from health insurance indications in Japan).

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Appendix I

Points to note about insured health services related to menopausal disorders and HRT in Japan
Appendix II
Questionnaire for HRT

See Table B1.

### Table B1 Questionnaire for hormone replacement therapy

For those of you who wish to undergo HRT:

In order to assess whether HRT can be administered safely, we ask you to please fill in the form accurately regarding the following questions.

- What is your current age? _____ years old
- When was your last menstruation (or how old were you)? _____ (year) _____ (month) _____ years old
- What is your current height / body weight?
  
  Height _____ cm  Body weight _____ kg
- Have you previously undergone HRT? Yes  No
  
  If “Yes”: From when to when? _____ (year) (month)~ _____ (year) (month)
  
  Did you have any problems? Yes  No
  
  What were the symptoms? 

- Are you currently receiving medical treatment by a physician? Yes  No
  
  If “Yes”: What is the disease name?

- Are you currently taking any medication or supplement? Yes  No
  
  If “Yes”: What is the name of the medicine/supplement?

- Have you ever had allergic symptoms (e.g., urticaria) after drug use? Yes  No
  
  If “Yes”: What is the name of the drug?

- Have you had any major disease in the past? Yes  No
  
  If “Yes”: What is the disease?

- Have you undergone surgery to remove your uterus? Yes  No

- Have you been told that you have liver function abnormalities, or have liver disease? Yes  No

(Continues)
Table B1  Continued

- Have you been diagnosed with breast cancer and undergone treatment?  
  Yes  No

- Has anyone in your family or relatives received a breast cancer diagnosis?  
  Yes  No

- Do you currently have a lump(s) in your breast?  
  Yes  No

- Have been diagnosed with gynecological cancer, particularly, cancer of the uterine body or ovary?  
  Yes  No

- Have you been told that you have uterine fibroids, endometriosis, or uterine adenomyosis?  
  Yes  No

- Do you currently have irregular bleeding from your vagina (abnormal vaginal bleeding) other than menstruation?  
  Yes  No

- Is there a possibility that you are currently pregnant?  
  Yes  No

- Do you currently have pain in the calves, swelling, sudden shortness of breath, chest pain, severe headache, fainting, blurred vision, or lisping, etc.?  
  Yes  No

- Have you had angina, myocardial infarction, stroke, cerebral hemorrhage, cerebral infarction, cerebrovascular disease, pulmonary thrombosis, venous thrombosis, or thrombophlebitis, etc.?  
  Yes  No

- Have you been told that your blood tends to clot easily by nature, or that you have a congenital thrombotic predisposition?  
  Yes  No

- Has anyone in your relatives suffered from thrombosis?  
  Yes  No

- Have you ever repeated abortion / stillbirth?  
  Yes  No

- Have you been told that you have pregnancy hypertensive syndrome or pregnancy toxemia during pregnancy?  
  Yes  No

- Are you scheduled for surgery in the near future, or have you recently undergone surgery?  
  Yes  No

- Have you been told that you have heart or kidney abnormalities?  
  Yes  No

(Continues)
Table B1 Continued

- Have you been told that you have abnormal lipid metabolism (e.g., hyperlipidemia)?
  - Yes
  - No

- Have you been told that your blood pressure is high?
  - Yes
  - No

- Have you been told that you have cholecystitis, or gallstones?
  - Yes
  - No

- Have you been told that you have diabetes mellitus, impaired glucose tolerance, or high blood glucose?
  - Yes
  - No

- Have you been told that you have migraines?
  - Yes
  - No

- Have you previously experienced a severe headache during the menstrual period or ovulation period?
  - Yes
  - No

- Have you been told you were epileptic?
  - Yes
  - No

- Have you been told that you have porphyria?
  - Yes
  - No

- Have you been told that you have systemic lupus erythematosus (SLE)?
  - Yes
  - No

- Please describe any other concerns and questions about your body or hormone replacement therapy (HRT) in the space below.

______ (year) _____ (month) ____ (day)

I declare the above descriptions are all correct.

Signature _______________________________