



Practice guidelines

Practice guideline for the treatment and management of iatrogenic premature ovarian insufficiency[☆]

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ABSTRACT

It is well known that premature ovarian insufficiency (POI) seriously affects the fertility, quality of life, and health of young women. A meta-analysis of global data indicated that the current population prevalence of POI is as high as 3.7 %, but exceeds 10 % in some countries and regions. When POI is caused by disease treatment, it is termed iatrogenic POI. Iatrogenic factors are the most common identifiable cause of POI, and iatrogenic POI has a high prevalence in young cancer survivors. Overall, iatrogenic POI accounts for approximately half of all cases, but data show that its prevalence in female cancer survivors under the age of 24 can reach up to 82.2 %. With the improvement of cancer treatment, this incidence is still rising. It arises in the context of a variety of diseases and has a complex etiology. Patients with iatrogenic POI tend to be younger than those with other types of POI, which means they can experience more harm from the condition, and there is an urgent need to diagnose, treat, and manage them as early as possible. However, there is currently no relevant consensus or guideline either within China or indeed internationally. This guideline expert group gathered data from doctors and patients in 34 provinces, municipalities, and autonomous regions across China through questionnaires to determine guideline-related issues and searched the literature in English-language databases such as Cochrane and PubMed since their establishment. After merging and deduplicating, literature evaluation and evidence grading were carried out. After discussion and induction, the clinical treatment and management guidelines for iatrogenic POI were formulated and combined with China's national conditions. The expert group ultimately addressed 19 clinical questions, as determined through a questionnaire survey and field investigation, and produced 26 recommendations based on international and domestic evidence from evidence-based medicine and clinical practice experience, to provide a reference for colleagues in clinical practice. The recommendations primarily reflect the context and needs within China and are intended for broad nationwide applicability, though regional adaptations based on local resources and practices may be necessary.

With medical technology's continuous development and progress, the cure and survival rates of malignant and refractory diseases have significantly improved in recent years. According to the World Health Organization (WHO), from 2000 to 2019, the global mortality rate of malignant tumors decreased by 16.4 % [1]. More than 4.82 million new cancers occurred in China in 2022 [2]. Cancer treatment can lead to the decline of ovarian function in girls and reproductive women. It is conservatively estimated that at least one million girls and women of reproductive women suffer from premature ovarian insufficiency (POI) due to radiotherapy and chemotherapy every year. POI is associated not only with impaired fertility but also with various general health issues, including cardiovascular disease, osteoporosis, psychosexual dysfunction, and genitourinary symptoms [3]. Consequently, various chronic diseases related to early menopause occur early, and the risk of

premature death is also significantly increased [4]. Therefore, protecting ovarian function and fertility during life-saving primary treatment requires a proactive approach from the healthcare team, involving patient counseling and supportive interventions. It is very important to take early prevention, treatment, and long-term management measures for iatrogenic POI.

POI is a disease characterized by loss of ovarian function. The disease was first described as "primary ovarian insufficiency" in 1942. Considering that "primary" is usually opposed to "secondary" and is easily confused with primary amenorrhea, in the 2016 guidelines of the European Society of Human Reproduction and Embryology (ESHRE), it is recommended to use "premature" to describe [3]. POI was once called "premature ovarian failure (POF)", but "failure" has the meaning of permanent loss. In patients with POI, ovarian function may still recover

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briefly.

Women who have abnormalities such as amenorrhea, oligomenorrhea, or frequent menorrhea before the age of 40, and the level of follicle-stimulating hormone (FSH) is greater than 25 U/L twice at an interval of 4 weeks, accompanied by a fluctuating decrease in estrogen levels, are diagnosed as POI [3,5–7]. The etiology of POI includes iatrogenic, genetic, immune, environmental, and other factors. Common causes of iatrogenic POI include surgery, radiotherapy, chemotherapy, and other treatments with ovarian toxicity or damage to ovarian function [5–8]. The American Society of Clinical Oncology (ASCO) guidelines stratify the risk of iatrogenic premature ovarian insufficiency (POI) into four categories: high risk (>80 % incidence of amenorrhea), intermediate risk (20–80 %), low risk (<20 %), and very low/no risk [9]. Importantly, both iatrogenic and non-iatrogenic causes of fertility loss necessitate comprehensive counseling on fertility preservation options and alternatives. For iatrogenic POI, the impact on fertility is highly variable, depending on the specific gonadotoxic agent and the patient’s age, thus requiring profoundly individualized management strategies [10].

Data from global Meta-analysis show that the current prevalence of POI is as high as 3.7 % and even exceeds 10 % in some countries and regions [11,12]. Iatrogenic POI accounts for about 50 % of POI patients [13]. With the improvement of cancer treatment, this incidence is still rising. Data show that the prevalence of POI among female cancer survivors younger than 24 years of age can reach up to 82.2 % [4,14]. Thus, iatrogenic POI stands as the most common identifiable cause of POI, significantly driven by its high prevalence in young cancer survivors and accounting for approximately half of all POI patients. It therefore seemed necessary to create a guideline specifically for “iatrogenic POI”, taking special account of the experience available in China. The reason is predictable. If ovarian tissue cryopreservation and transplantation (OTCT) technology is adopted before disease treatment, iatrogenic POI can be prevented and treated. For details, please refer to the Clinical Application Guidelines of Ovarian Tissue Cryopreservation and Transplantation for Prevention and Treatment of Iatrogenic POI [15]. Still, many people lose the opportunity for ovarian function and fertility preservation due to various reasons. Patients who have clinically developed iatrogenic POI are often adolescents and women of child-bearing age. The sudden occurrence of menopause, the related symptoms, and chronic diseases caused by early menopause are ten, twenty, or even earlier, which has a huge impact on the fertility and life of patients. Health has an urgent need for early treatment and management. At present, there is still a lack of guiding opinions on the prevention and management of iatrogenic POI at home and abroad.

The working group of this guideline organized multidisciplinary experts to distribute more than 1000 questionnaires to doctors and patients in 34 provinces, municipalities, and autonomous regions across the country. According to the questionnaire survey results, the scientific issues related to the guideline were determined, and the literature included in the English databases of Cochrane, Pubmed, Embase, Science, etc., were searched since the establishment of the database. Keywords include “POI”, “iatrogenic POI”, “POF”, “early menopause”, “surgical menopause”, “cancer survivor”, “hormone replacement therapy (HRT)”, “fertility preservation (FP)”, etc. After merging and deduplication, the literature was evaluated, and the evidence was graded according to the Oxford Center for Evidence-Based Medicine, England standards. According to the international and domestic evidence-based medicine evidence and clinical practice experience, combined with China’s national conditions, the guidelines for clinical treatment and management of iatrogenic POI were formulated after discussion and summary by the guidelines working group. This guideline comprises questions and recommendations and gives 26 recommendations for the 19 clinical questions raised. The purpose is to guide the prevention and management of iatrogenic POI. The evidence level (Table 1) and recommendation level (Table 2) of this guideline refer to the standard of the Oxford Center for Evidence-Based Medicine 2009 [16] and are

Table 1
The level and meaning of evidence used in this guide.

Level of evidence	Meaning
1a	Homogeneous randomized controlled trials, initial cohort, prospective cohort, systematic review of level 1 diagnostic studies, multi-population based studies, multicenter studies
1b	Randomized controlled trial with a narrow confidence interval, follow-up >80 %, single population, single-center study
1c	Evidence that the observation result is “all or no.”
2a	A systematic review of homogeneous cohort studies, retrospective cohorts of randomized controlled studies, and diagnostic studies above grade 2
2b	1 cohort (including low-quality randomized controlled studies), retrospective cohort, poor follow-up
2c	Outcome study
3a	Systematic review of homogeneous case-control studies
3b	1 case-control study, discontinuous study
4	Case series study, low-quality cohort study, or case-control study
5	Expert opinion, no clear, rigorous evaluation, basic research based on laboratory

Table 2
Recommended levels and meanings used in this guide.

Recommended grade	Meaning
A	Consistent Level 1 evidence
B	Consistent Level 2 or Level 3 evidence or inference of Level 1 evidence
C	Level 4 evidence, or level 2 or level 3 evidence inference
D	Level 5 evidence, or inconsistent or uncertain conclusions

marked in brackets after each recommendation. See Table 3 for details of all recommended clauses in this guideline.

1. Common cause of iatrogenic POI

1.1. What are the procedures at risk of iatrogenic POI?

Surgeries that lead to iatrogenic POI mainly include surgeries that require partial or total ovarian resection due to malignant diseases or may affect ovarian blood supply and cause ovarian function damage. Surgery for benign ovarian diseases, including ovarian cyst pedicle torsion and ovarian endometriosis, can also significantly affect ovarian function. Studies have shown that after endometriosis cyst removal, anti-müllerian hormone (AMH) decreased significantly [17], and the degree of decrease was related to the scope of endometriosis, cyst size, surgical method, etc [18]. Bilateral ovarian surgery is more risky than unilateral surgery and easily leads to POI [19].

Some women with high risk of tumors, such as carriers of BRCA gene mutations, may undergo “Risk-reducing” bilateral salpingo-oophorectomy (BSO) to reduce the risk of ovarian cancer and breast cancer [20,21]. However, while reducing the risk of cancer, it causes iatrogenic premature menopause and increases all-cause mortality. A population-based long-term follow-up study found that patients undergoing hysterectomy due to tumor risk, if both ovaries are prophylactically removed at the same time, will increase all-cause mortality in women under 50 years old, especially in patients under 45 years old with iatrogenic POI and early menopause [22]. It is worth noting that surgical menopausal patients have more severe menopausal symptoms than natural menopausal women and may increase the risk of Parkinson’s disease and cognitive impairment [23–25].

Although hysterectomy and tubal sterilization do not cause POI, they are still associated with early menopause [26,27]. Uterine artery embolization may also have the risk of causing ovarian hypofunction. However, it mainly occurs in patients over 45 years of age, and the risk of POI in women under 40 years of age is small [28].

Table 3

See the following table for all recommended items in this practice guideline.

Recommended content	Quality of evidence	Recommended strength
1. Common causes of iatrogenic POI		
Recommendation 1–1: Increased risk of iatrogenic POI in ovarian endometriosis surgery. Patients should be informed of this risk before surgery and advised to consult the methods of ovarian function and fertility protection and preservation.	1b	A
Recommendation 1–2: For young or future patients with malignant tumors of the reproductive system who have fertility needs, the effect of surgery on ovarian function should be informed before surgery, and patients should be advised to consult the methods of ovarian function and fertility protection and preservation.	1b	A
Recommendation 1–3: BRCA mutation carriers should be fully informed that although ovariectomy can reduce the risk of ovarian cancer and breast cancer, it will lead to early menopause and may lead to an increase in all-cause mortality. Patients should be informed to consult the methods of ovarian function and fertility protection and preservation before surgery.	1b	A
Recommendation 1–4: Patients or their guardians should be informed before radiotherapy of the serious effects of radiotherapy, especially pelvic radiotherapy, on ovarian function. It is recommended to consult ovarian function and fertility protection and preservation before radiotherapy.	2b	B
Recommendation 1–5: Before chemotherapy, it is recommended to inform patients or guardians of the risk of iatrogenic POI and to consult ovarian function and fertility protection and preservation.	2b	B
Recommendation 1–6: Although hematopoietic stem cell transplantation (HSCT) is usually very urgent because this treatment can cause serious damage to ovarian function, once the primary disease determines that HSCT is needed, the patient or guardian should be told as soon as possible for consultation on ovarian function and fertility protection and preservation.	2b	B
2. Prevention of iatrogenic POI and fertility preservation		
Recommendation 2–1: The effect of ovarian transposition on protecting ovarian function is very limited. Before radiotherapy, patients must be informed to consult other, more effective methods of ovarian function and fertility protection and preservation.	2b	B
Recommendation 2–2: GnRHa is not recommended as the preferred regimen for preserving ovarian function in cancer patients.	3b	B
Recommendation 2–3: Bilateral salpingo-oophorectomy (BSO) to reduce the risk of ovarian cancer and breast cancer should be carried out carefully, with full consideration of the patient's genetic etiology, age, fertility requirements, and other factors. It is not recommended to perform surgery solely because of a family history of cancer.	2b	B
Recommendation 2–4: Oocyte and/or embryo freezing techniques can be used for fertility preservation in individuals at high risk of iatrogenic POI.	1b	A

Table 3 (continued)

Recommended content	Quality of evidence	Recommended strength
Recommendation 2–5: Ovarian tissue cryopreservation and transplantation are the most important methods to prevent and treat iatrogenic POI. It is suitable for the protection of ovarian function and fertility of tumor and non-tumor patients. It is the main method to protect the ovarian function and fertility of prepubertal girls and women of reproductive age whose treatment of gonadal toxicity cannot be delayed.	2b	B
3. Comprehensive diagnosis, treatment, and long-term management of patients with iatrogenic POI		
Recommendation 3–1: People at high risk of iatrogenic POI should pay attention to the monitoring of ovarian reserve function. Medical history combined with FSH, AMH, and pelvic ultrasound can be used to evaluate and follow up ovarian reserve function.	1a	A
Recommendation 3–2: Patients with iatrogenic POI should be informed that hormone replacement therapy (HRT) can protect bone, cardiovascular, and brain health.	2b	B
Recommendation 3–3: Before choosing HRT, patients with iatrogenic POI should combine the characteristics of the primary disease, exclude the contraindications of HRT, evaluate the risks and benefits, and formulate an individualized plan.	3b	C
Recommendation 3–4: It is recommended that patients with iatrogenic POI start HRT as soon as possible after the end of primary disease treatment if there is no contraindication and continue at least until the average age of natural menopause.	2b	B
Recommendation 3–5: Patients with uterus need a combination of estrogen and progesterone therapy to prevent endometrial lesions.	1q	A
Recommendation 3–6: For patients with a high risk of thrombosis, percutaneous estrogen can be considered, which has better safety than oral estrogen.	2b	B
Recommendation 3–7: When iatrogenic POI needs to be induced by puberty, it is recommended to start as soon as possible after the age of 10, and the estrogen dose gradually and slowly increases.	2b	B
Recommendation 3–8: Traditional Chinese medicine, which has been verified by many randomized controlled trials (RCTs), may be effective in the treatment of iatrogenic POI and can be used as a choice to relieve hot flashes and sweating in patients who are contraindicated or unwilling to use HRT.	2b	B
4. HRT in patients with different primary iatrogenic POI		
Recommendation 4–1: Patients with vulvar, vaginal, and cervical squamous cell carcinoma can improve menopausal symptoms through systemic or local HRT.	1a	A
Recommendation 4–2: For survivors of cervical adenocarcinoma and adenosquamous carcinoma, HRT should be considered with extreme caution. If used, it requires individualized risk-benefit evaluation, reference to principles for endometrial adenocarcinoma, and close monitoring.	3b	C

(continued on next page)

Table 3 (continued)

Recommended content	Quality of evidence	Recommended strength
Recommendation 4-3: Survivors of early low-risk endometrial cancer use HRT after surgery, and their recurrence rate is very low. Individualized programs are needed, but patients' informed consent and close follow-up must be obtained.	3b	C
Recommendation 4-4: HRT can improve the overall survival rate of patients with epithelial ovarian cancer after surgery and improve the quality of life of patients with advanced-stage epithelial ovarian cancer. Clinicians can consider recommending individualized HRT regimens according to the condition, pathological type, stage, grade, and hormone sensitivity of the tumor.	2b	B
Recommendation 4-5: Patients with iatrogenic POI because of endometriosis need to choose an individualized HRT regimen according to the severity of the disease. It is recommended that the continuous or similar combination regimen be the first choice.	3b	C
Recommendation 4-6: BRCA mutation carriers without a history of breast cancer may consider HRT to relieve menopausal symptoms after BSO.	3b	B
Recommendation 4-7: Breast cancer survivors usually do not recommend HRT, and patients with genitourinary tract syndrome may consider topical application of estrogen to improve symptoms.	3b	B

1.1.1. Recommendation 1-1

Increased risk of iatrogenic POI in ovarian endometriosis surgery. Patients should be informed of this risk before surgery and advised to consult the methods of ovarian function and fertility protection and preservation (1b, A).

1.1.2. Recommendation 1-2

For young or future patients with malignant tumors of the reproductive system who have fertility needs, the effect of surgery on ovarian function should be informed before surgery, and patients should be advised to consult the methods of ovarian function and fertility protection and preservation (1b, A).

1.1.3. Recommendation 1-3

BRCA mutation carriers should be fully informed that although ovariectomy can reduce the risk of ovarian cancer and breast cancer, it will lead to early menopause and may lead to an increase in all-cause mortality. Patients should be informed to consult the methods of ovarian function and fertility protection and preservation before surgery (1b, A).

1.2. Is radiotherapy likely to cause iatrogenic POI?

The influencing factors leading to iatrogenic POI after radiotherapy include the site, extent, dose, and age [29–31]. Among them, the risk of POI in patients with bilateral ovaries in the irradiated area is 19.7 times higher than that in patients with ovaries not in the irradiated area [32]. In women under 20 years old, a radiotherapy dose of 2 Gy can halve the number of oocytes, a radiotherapy dose of 6 Gy may lead to irreversible damage to ovarian fertility, and a radiotherapy dose of 20–26 Gy can lead to POI [33–35]. The irradiation dose threshold of POI induced by radiotherapy decreases with the increase of patient age. According to the model calculation, in infancy, 10, and 20 years old, the radiotherapy dose thresholds for POI were 20.3 Gy, 18.4 Gy, and 16.5 Gy in turn [29].

The American Society of Clinical Oncology (ASCO) believes that radiotherapy exposure doses exceeding 15 Gy in prepubertal girls, 10 Gy in adolescence, and 4–6 Gy in adult women are at high risk of POI [36,37]. An irradiation dose of 8 Gy in 40-year-old women can cause ovarian function failure [34].

1.2.1. Recommendation 1-4

Patients or their guardians should be informed before radiotherapy of the serious effects of radiotherapy, especially pelvic radiotherapy, on ovarian function. It is recommended to consult ovarian function and fertility protection and preservation before radiotherapy (2b, B).

1.3. Is chemotherapy likely to cause iatrogenic POI?

The toxicity of chemotherapeutic drugs to the gonads depends on factors such as drug type, dose, combination regimen, duration of use, disease severity, and patient age [38]. Alkylating agents commonly used in chemotherapy are gonadotoxic [39]. The application of alkylating agents alone can lead to a 9.2-fold increase in the risk of POI, and the combined radiotherapy and chemotherapy based on alkylating agents will lead to a 27-fold increase in the risk of POI [40]. Long-term follow-up of children cancer survivors (CCS) shows that after treatment with alkylating agents, the ovarian reserve and reproductive capacity of survivors are lower than those without treatment with alkylating agents [41,42]. Studies have suggested that when the equivalent dose of cyclophosphamide (CED) is $\geq 4 \text{ g/m}^2$, ovarian function will be significantly impaired [37]. The risk of ovarian function damage caused by drugs such as cyclophosphamide and doxorubicin is also related to patient age and cumulative dose [36,43]. Common chemotherapy drugs and their CEDs with high (>80 %) and intermediate (20–80 %) risk of POI are detailed in Table 4. The risk of POI caused by a combined chemotherapy regimen is related to the type of primary disease. Table 5 lists primary disease and combination chemotherapy regimens with a higher risk of POI.

1.3.1. Recommendation 1-5

Before chemotherapy, it is recommended to inform patients or guardians of the risk of iatrogenic POI and to consult ovarian function and fertility protection and preservation (2b, B).

1.4. Is it necessary to consider ovarian function and fertility preservation before HSCT?

HSCT is an important method for treating hematological diseases (especially hematological malignancies) and congenital or hereditary diseases. However, a myeloablative conditioning regimen (MAC) before transplantation requires super-dose radiotherapy and chemotherapy. Among them, the commonly used dose of cyclophosphamide can reach 3.6 g/m^2 , much higher than the dose of 0.75 g/m^2 commonly used in

Table 4
Common chemotherapy drugs at risk of POI [36,37,43,44].

High-risk drugs and their CED	Medium-risk drugs
Cyclophosphamide* Cumulative dose under 20 years of age $>7.5 \text{ g/m}^2$	Cyclophosphamide* The cumulative dose between 30 and 39 years old reaches 5 g/m^2
Cumulative dose over 40 years old $>5 \text{ g/m}^2$	Cisplatin
Busulfan $>0.5 \text{ g/m}^2$	Carboplatin
Chlorambucil $>0.3 \text{ g/m}^2$	Paclitaxel
Ifosfamide $>16 \text{ g/m}^2$	Bevacizumab
Melphalan $>0.1 \text{ g/m}^2$	Doxorubicin 30–40 years old
Nitrosourea $>0.3 \text{ g/m}^2$	
Benzyl hydrazine $>5 \text{ g/m}^2$	
Doxorubicin over 40 years old	

Note: *The risk of cyclophosphamide causing POI in women aged 20 to 30 years is lower than that in women over 30 years old, but it is related to specific combination chemotherapy regimens.

Table 5

Primary disease and combination chemotherapy regimens with higher risk of POI [37,44–49].

Primary disease	Chemotherapy regimens	Estimating POI risk
Hodgkin's lymphoma	MOPP	10 %–50 %
	BEACOPP (8 cycles)	50 %–95 % (age-related)
Breast cancer	CMF (8 cycles)	>80 % (≥ 40 years old)
	CEF (6 cycles)	30 %–70 % (30–39 years old)
	CAF (6 cycles)	30 %–70 % (30–39 years old)
	AC (4 cycles)	30 %–70 % (≥ 40 years old)
		>20 % (30–39 years old)

Note: MOPP: Nitrogen mustard + vincristine + prednisone + methylhydrazine; BEACOPP: Bleomycin + etoposide + doxorubicin + cyclophosphamide + vincristine + prednisone + methylhydrazine; CMF: Cyclophosphamide + methotrexate + fluorouracil; CEF: Cyclophosphamide + epirubicin + fluorouracil; CAF: Cyclophosphamide + doxorubicin + fluorouracil; AC: Adriamycin + cyclophosphamide.

treating hematological diseases [50]. The radiotherapy irradiation dose can reach 12 Gy [51]. These will cause serious and irreversible damage to the patient's ovaries. According to statistics, the number of HSCTs is increasing yearly, and the number of transplants worldwide has exceeded 50,000 yearly [52]. Among HSCT patients in China, 42 % were female, and 31 % were no older than 18 years [53]. HSCT makes the survival rate of some diseases reach more than 90 % [54], but more than 70 % of female patients develop POI after HSCT, including 62.5 % of women aged 11–20 and 100 % of women aged 21–40 [55,56]. The pregnancy rate after HSCT in female patients is less than 5 % [57]. Paying attention to the fertility preservation of girl patients and preserving ovarian function before HSCT pretreatment requires multidisciplinary cooperation and joint efforts.

1.4.1. Recommendation 1–6

Although HSCT is usually very urgent because this treatment can cause serious damage to ovarian function, once the primary disease determines that HSCT is needed, the patient or guardian should be told as soon as possible for consultation on ovarian function and fertility protection and preservation (2b, B).

2. Prevention of iatrogenic POI and fertility preservation

2.1. Can ovarian transposition preserve ovarian function?

To prevent POI caused by pelvic radiotherapy, the main method of traditional ovarian preservation is ovarian transposition. In the past, it was believed that for patients with low risk of ovarian metastasis and non-hormone dependence, it was considered to displace the ovaries to the bilateral paracolic sulcus, with a height at least higher than the level of the bilateral iliac crest connection, to reduce the damage of ovarian function by radiotherapy. Ovarian transposition combined with pelvic lead barrier shielding gonads can reduce ovarian damage caused by radiotherapy [58]. However, POI may still occur after ovarian transposition [59].

Whether ovarian transposition can prevent POI is related to the location of the displaced ovary, the type of radiotherapy, irradiation dose, scattering, reflection, whether the gonadal barrier is increased, age, etc. Placing the ovary outside the pelvic cavity, brachyirradiation, and adding a lead barrier may reduce the damage to gonads caused by radiotherapy. However, at present, the follow-up time of most related studies is short, and there is significant heterogeneity in systematic analysis [54]. Studies have shown that ovarian transposition combined with pelvic radiotherapy can maintain normal ovarian function in about 65.3 % of patients 1 year after treatment, but it will drop to 38.5 % after 5 years [60]. A long-term follow-up of cervical cancer patients showed that the mean menopausal age of non-radiotherapy patients without ovarian transposition or unilateral oophorectomy was 50.6 years, that of

non-radiotherapy patients with ovarian displacement was 45.8 years, and that of patients with ovarian transposition combined with pelvic radiotherapy was 36.6 years, Ovarian transposition is not effective in reducing the risk of POI [61].

2.1.1. Recommendation 2–1

The effect of ovarian transposition on protecting ovarian function is very limited. Before radiotherapy, patients must be informed to consult other, more effective methods of ovarian function and fertility protection and preservation (2b, B).

2.2. Does GnRHa have a preventive effect on iatrogenic POI?

It has been suggested that gonadotropin-releasing hormone agonist (GnRHa) can reduce the primary follicles entering the growth pool by inhibiting the ovaries, thereby reducing the sensitivity of follicles to gonadotoxic drugs and protecting the ovaries [62]. Randomized clinical trials have shown that for chemotherapy patients with premenopausal breast cancer, GnRHa may reduce the risk of POI to some extent [63]. However, in hematological malignancies, a prospective randomized study with a follow-up of more than 5 years showed that GnRHa did not reduce the risk of POI caused by HSCT or cyclophosphamide accumulation [64]. A Cochrane study included 12 RCTs in 1369 women undergoing chemotherapy, including breast cancer, ovarian cancer, lymphoma, etc. The results found that after 12 months of follow-up, there was no significant difference in menstrual recovery or maintenance rate and pregnancy rate between the GnRHa group and the control group (326/447 vs. 276/422, or 72.9 % vs. 65.4 %, $p = 0.24$; 32/356 vs. 22/347, or 9 % vs. 6.3 %, $p = 0.09$) [65]. The clinical practice guidelines for fertility preservation in cancer patients issued by ASCO believe that the evidence of GnRHa protecting fertility is insufficient, and it is not recommended to use GnRHa as the first choice for fertility preservation in cancer patients. Only when effective fertility preservation methods, such as oocyte cryopreservation, embryo cryopreservation, or ovarian tissue cryopreservation (OTC) are not available is this method considered in young women with breast cancer [66,67].

2.2.1. Recommendation 2–2

GnRHa is not recommended as the preferred regimen for preserving ovarian function in cancer patients (3b, B).

2.3. Should people at high risk of ovarian or breast cancer undergo bilateral oophorectomy to prevent cancer?

Ovarian cancer is not easy to detect early, and the prognosis is often poor when found, so some high-risk people will choose opportunistic BSO. A large long-term cohort study of hysterectomy for benign diseases showed that the cumulative incidence of ovarian cancer in patients with “opportunistic” BSO and patients with ovary preservation was 0.08 % and 0.46 %, respectively, and BSO significantly reduced the risk of ovarian cancer in women [68]. However, after ovariectomy, the impaired endocrine function of women can also damage women's health. Therefore, the indications and population of preventive surgery have been controversial. Due to the lack of a uniform definition or consensus of “family history of cancer”, a “family history” of ovarian or breast cancer is not a reason to remove both ovaries. However, it can be a reason for genetic testing. Genes at high risk of tumors in women include BRCA1/2, RAD51C/D, BRIP1, PALB2, MLH1, MSH2/6, etc [69]. Among these gene variants, BRCA1 and BRCA2 are the most common risk genes for ovarian and breast cancer [70]. Women with BRCA1 mutation have a 44 % risk of ovarian cancer and 72 % risk of breast cancer by the age of 70; Women with BRCA2 mutations were 17 % and 44 %, respectively [71]. Guidelines in many countries suggest that the relationship between morbidity risk and age should be considered before implementing BSO. The National Comprehensive Cancer Network (NCCN) recommends that if fertility needs are not considered,

patients with BRCA1 mutations can undergo BSO at 35–40 years old, and patients with BRCA2 mutations can undergo BSO at 40–45 years old. However, the treatment of fertility and menopausal symptoms in postoperative patients is still controversial, and individualized plans should be formulated [72].

2.3.1. Recommendation 2–3

Bilateral salpingo-oophorectomy (BSO) to reduce the risk of ovarian cancer and breast cancer should be carried out carefully, with full consideration of the patient's genetic etiology, age, fertility requirements, and other factors. It is not recommended to perform surgery solely because of a family history of cancer (2b, B).

2.4. What are the main methods of fertility preservation in patients at high risk of iatrogenic POI? How do I make a selection?

The main methods of fertility preservation in patients with a high risk of iatrogenic POI include oocyte freezing, embryo freezing, and OTC. These three methods have been officially used clinically and have achieved encouraging results in terms of pregnancy rate and live birth rate. They have been approved by the American Society for Reproductive Medicine (ASRM), ESHRE, and the Society for Assisted Reproductive Technology (SART) Practice Committee is no longer an experimental technology [73–75].

It is worth noting that although oocyte and embryo freezing can be applied to fertility preservation in high-risk groups of iatrogenic POI because both methods require superovulation, they are not suitable for patients who need emergency treatment and prepubertal patients, and embryo freezing requires sperm, so it is suitable for married patients. OTC technology does not require ovarian stimulation and does not delay the treatment of primary disease, which is the main method to protect the fertility of prepubertal girls. Cryopreserved ovarian tissue transplantation can restore the ovarian endocrine function of patients and can obtain pregnancy and live birth, which is one of the standard fertility preservation methods [74]. In some countries, cryopreservation ovarian tissue transplantation can also be used in healthy women to prolong the reproductive window and delay the menopausal age [76]. Studies have shown that the age at cryopreservation and the number of oocytes in the ovary are the main factors affecting the pregnancy rate and endocrine recovery effect after transplantation [77]. For details, please refer to “Practice guideline of ovarian tissue cryopreservation and transplantation in the prevention and treatment of iatrogenic premature ovarian insufficiency” [15].

The fertility preservation of patients at risk of iatrogenic POI should run through the diagnosis and treatment of primary disease. Iatrogenic POI is a serious threat to women's health, so it is necessary to pay attention to its prevention. Before any treatment that affects patients' ovarian function, patients should be fully informed of the risk of iatrogenic POI. After treatment, we should focus on the long-term follow-up of ovarian function, find problems, and deal with them in time. Departments related to diagnosing and treating primary diseases, gynecological endocrinology, reproductive medicine, and other disciplines must work together to help patients and their families obtain more medical resources and information to make reasonable medical choices.

2.4.1. Recommendation 2–4

Oocyte and/or embryo freezing techniques can be used for fertility preservation in individuals at high risk of iatrogenic POI (1b, A).

2.4.2. Recommendation 2–5

Ovarian tissue cryopreservation and transplantation are the most important methods to prevent and treat iatrogenic POI. It is suitable for the protection of ovarian function and fertility of tumor and non-tumor patients. It is the main method to protect the ovarian function and fertility of prepubertal girls and women of reproductive age whose treatment of gonadal toxicity cannot be delayed (2b, B).

3. Comprehensive diagnosis, treatment, and long-term management of patients with iatrogenic POI

3.1. How is ovarian reserve function assessed?

Risk groups and patients with iatrogenic POI need to evaluate and monitor ovarian function. Women may still have regular periods before their ovarian function decreases [78]. Estradiol levels in patients with POI may fluctuate and are not reliable for ovarian function assessment. National guidelines generally recommend two FSH tests, at least 4 weeks apart, to establish the diagnosis of POI [5].

AMH may have declined before FSH fluctuates or menstruation changes [79]. AMH is secreted by growing preantral follicles and minor antral follicles, which is low in childhood, rises to a peak after child-bearing age, and then gradually decreases. In women younger than 36 years, AMH < 1.1 ng/mL is a risk factor for POI [80]. AMH levels can detect decreasing ovarian reserves (DOR) and POI in children and women of childbearing age [81]. Meta-analysis shows that even in patients of different ages and different primary diseases, a rapid decline in AMH can be observed after the start of cancer treatment [82,83]. It is recommended to monitor patients' AMH levels before and after cancer treatment to assess the degree of ovarian damage in patients for timely treatment [84].

Pelvic ultrasound measures the ovarian size and follicle number and is an important method for evaluating ovarian function. When AFC is less than 5–10, it suggests decreased ovarian reserve function; when AFC is 0–2, it suggests POI [85].

3.1.1. Recommendation 3–1

People at high risk of iatrogenic POI should pay attention to the monitoring of ovarian reserve function. Medical history combined with FSH, AMH, and pelvic ultrasound can be used to evaluate and follow up ovarian reserve function (1a, A).

3.2. Why is it necessary to assess the risk of hormone replacement therapy in patients with iatrogenic POI?

POI has serious health implications for patients. In patients with surgical menopause, menopausal symptoms tend to be more severe than in women with natural menopause due to a sudden drop in hormone levels [86,87]. For young patients with iatrogenic POI, the goal of hormone replacement therapy (HRT) is to provide physiological doses of hormone replacement to maintain long-term health. Its estrogen dose is usually higher than routine menopausal hormone therapy (MHT) and the preferential transdermal route of administration is recommended to optimize safety. HRT can improve estrogen deficiency symptoms, including hot flashes, sweating, irritability, insomnia, etc. It can delay the occurrence and development of chronic diseases related to early menopause, including osteoporosis, fracture, genitourinary tract atrophy, cardiovascular diseases, etc. [88], which is the most effective method to treat hypoestrogenemia. However, the etiology of patients with iatrogenic POI is complex, so a comprehensive examination should be conducted before applying HRT for benefit and risk assessment. HRT does not provide contraception, women with non-surgical POI should be advised to use contraception if they wish to avoid pregnancy, although patients with iatrogenic POI are less likely to become pregnant [5].

HRT of patients with iatrogenic POI should fully consider the characteristics of the primary disease. After the primary disease is fully treated, the contraindications of HRT should be ruled out through comprehensive examination, and the benefits and risks of HRT should be assessed. Pay attention to the patient's primary disease risk and new tumor recurrence. Discuss and analyze with multidisciplinary collaboration, and adopt multi-level individualized health care treatment and long-term management. Not all tumors are contraindications to HRT. Individualized treatment plans should be formulated according to the type, age, and evidence-based medicine data of tumors or diseases to

balance the benefits and risks of patients.

3.2.1. Recommendation 3–2

Patients with iatrogenic POI should be informed that hormone replacement therapy (HRT) can protect bone, cardiovascular, and brain health (2b, B).

3.2.2. Recommendation 3–3

Before choosing HRT, patients with iatrogenic POI should combine the characteristics of the primary disease, exclude the contraindications of HRT, evaluate the risks and benefits, and formulate an individualized plan (3b, C).

3.3. What are the guiding principles for HRT in patients with iatrogenic POI?

To prevent the impact of low estrogen on health, HRT for patients with iatrogenic POI should be started as soon as possible without affecting the risk of primary disease and last, at least until the average natural menopausal age, that is, around 50 years old [89,90], and then managed according to the protocol of MHT. The purpose of hormone therapy is physiological replacement. Since patients with iatrogenic POI are mostly young women in adolescence and childbearing age, the demand for estrogen should be individually formulated and selected according to different age groups, different primary diseases, and whether there are fertility requirements.

HRT is divided into estrogen alone therapy and estrogen and progesterone combination therapy. Estrogen therapy alone is mainly suitable for patients without uterine and puberty-induced secondary sexual characteristics. Estrogen supplementation mainly includes oral and transdermal. Commonly used oral estrogens include conjugated estrogen 0.625 mg/d and estradiol valerate 1–2 mg/d. Currently, commonly used transdermal estrogens are mainly 17 β -estradiol gel 1.25–2.5 g/d (including 17 β -estradiol 0.75–1.5 mg/d) in China [91,92]. For women with uterus, combined therapy with estrogen and progesterone is required. The most commonly used regimen is a continuous sequential regimen, such as 17 β -estradiol/17 β -estradiol dydrogesterone (1/10 or 2/10 dosage form) 1 tablet/day, for patients with endometriosis or who do not want to have withdrawal bleeding, a continuous combination regimen can be considered, such as 17 β -estradiol/drospirenone (1 mg/2 mg) 1 tablet/day, tibolone 1.25–2.5 mg/d, etc. It is recommended that patients with POI take long-term estrogen supplementation to avoid symptoms of estrogen deficiency and related diseases. Non-oral (such as transdermal) estrogens can avoid first-pass effects in the liver, achieve higher estrogen levels at lower doses, and are more suitable for some patients who may have potential thrombotic risk factors such as smoking [93]. Topical estrogen therapy, such as conjugated estrogen cream, promestriene vaginal capsules, or creams, among others, can be used for vulvovaginal atrophy or genitourinary syndrome [94]. Modes of administration of progestogens include oral, transvaginal. For women of childbearing age with uterus, the application of progestogens per cycle is at least 10 to 14 days.

3.3.1. Recommendation 3–4

It is recommended that patients with iatrogenic POI start HRT as soon as possible after the end of primary disease treatment if there is no contraindication and continue at least until the average age of natural menopause (2b, B).

3.3.2. Recommendation 3–5

Patients with uterus need a combination of estrogen and progesterone therapy to prevent endometrial lesions (1a, A).

3.3.3. Recommendation 3–6

For patients with a high risk of thrombosis, percutaneous estrogen can be considered, which has better safety than oral estrogen (2b, B).

3.4. How to induce puberty in girls with iatrogenic POI?

Prepubertal girls with damaged gonads may develop iatrogenic POI before puberty. Some patients' ovarian function even fails before puberty, and primary amenorrhea occurs, which requires puberty induction. Because such patients are more prone to metabolic syndrome, bone mineral density reduction, and estrogen deficiency-related diseases or symptoms [95], the impact is far-reaching, and attention should be paid to the management of their whole life cycle. Its prevention, treatment, and long-term management strategies can refer to the experience of girls with Turner Syndrome (TS) [96,97]. The ovarian function should be monitored regularly, and patients with a high risk of POI should try to preserve reproductive and endocrine functions by cryopreserving ovarian tissue when the ovaries are not damaged or still functional [15].

Girls with POI start low-dose estrogen replacement therapy after 10 years of age to induce secondary sexual characteristics, and if necessary, puberty can be caused by transplanting cryopreserved ovarian tissue [15,96,97]. The low-dose estrogen regimen did not affect the height of patients in adulthood [98]. Since natural estrogen has little effect on blood coagulation, blood lipids, and blood pressure, it is recommended to choose natural estrogen as much as possible [99]. The starting dose is 1/10 to 1/8 of the adult dose, with the option of 17 β -estradiol 5 μ g/kg/d or 0.25 mg/d orally, or 6.25 μ g/d transdermally. The dose was increased every 6–12 months over 2–4 years, gradually to an adult dose, i.e., 17 β -estradiol 2–4 mg/d orally or 100–200 μ g/d transdermally, mimicking the course of female puberty [98,100]. Progestogens is added after 1–2 years of estrogen use or when breakthrough bleeding occurs. Dydrogesterone 10 mg/d, or oral micronized progesterone 100–200 mg/d, 12–14 days per month, can be selected [101]. For patients with a late diagnosis of POI, individualized plans can be formulated according to age, height, etc. Girls with iatrogenic POI still need to continue hormone replacement therapy after the induction of puberty, at least until the age of natural menopause in normal women [97].

3.4.1. Recommendation 3–7

When iatrogenic POI needs to be induced by puberty, it is recommended to start as soon as possible after the age of 10, and the estrogen dose gradually and slowly increases (2b, B).

3.5. What is the effectiveness and safety of traditional Chinese medicine, herbal medicine, and other non-hormonal methods in treating iatrogenic POI?

Some patients with iatrogenic POI may have contraindications to HRT, may not be suitable for the application of estrogenic drugs temporarily, or may choose non-hormonal drugs such as traditional Chinese medicine (TCM) or herbal medicine due to concerns. Previous research showed that the Kuntai capsule has certain efficacy in improving the symptoms of low estrogen in patients with POI [102], and the mechanism has been verified in animal experiments [103], which can be used as adjuvant therapy for patients with iatrogenic POI. It is important to note that while some TCM treatments are supported by clinical experience and preliminary studies within specific regions, the precise mechanisms, active compounds, and standardized dosages for many formulations remain to be fully elucidated. Further rigorous, multi-center clinical trials are required to validate their efficacy and safety in broader populations. Black cohosh relieves vasomotor symptoms in Europe and America, but its effectiveness has not been fully demonstrated [104]. Since there have been cases of hepatotoxicity of black cohosh [105], its safety needs to be further confirmed.

In addition to TCM and herbal medicine, other non-hormonal treatments can also be considered according to different menopausal symptoms. Such as selective serotonin reuptake inhibitors, clonidine, gabapentin, etc., may help improve hot flashes. Acupuncture, massage, physiotherapy, yoga, cognitive behavioral therapy, etc., can also help alleviate symptoms related to estrogen deficiency [106]. Soap-free

detergents, moisturizers, lubricants, etc., may be considered for patients with vulvovaginal atrophy.

In addition to HRT, the prevention and treatment of osteoporosis also includes calcium supplementation, vitamin D, bisphosphonates, denosumab, etc., as appropriate [107]. Multicenter randomized double-masked controlled studies have shown that denosumab 60 mg, subcutaneously injected every 6 months, has a good long-term safety profile for postmenopausal osteoporosis [108–110].

3.5.1. Recommendation 3–8

Traditional Chinese medicine which has been verified by many randomized controlled trials (RCTs), may be effective in the treatment of iatrogenic POI and can be used as a choice to relieve hot flashes and sweating in patients who are contraindicated or unwilling to use HRT (2b, B).

4. HRT in patients with different primary iatrogenic POI

4.1. Can survivors of vulvar, vaginal, and cervical cancer consider HRT?

With the popularization of cervical cancer screening, most cases can be diagnosed at the early stage, yielding a survival rate of up to 95.9 % [111]. As cervical cancer frequently occurs in women of reproductive age, many survivors may need to consider HRT for management of menopausal symptoms. According to the 2020 joint position statement from the European Menopause and Andropause Society (EMAS) and the International Gynecologic Cancer Society (IGCS) on menopausal management after gynecological cancer [112]: vulvar cancer, vaginal cancer, and cervical squamous cell carcinoma are not hormone-dependent and can be treated with systemic or local HRT. However, studies indicate that less than half of patients may be willing to undergo HRT [113], and patients should be fully informed that HRT does not increase the risk of disease recurrence and can effectively alleviate symptoms. It is important to note that cervical cancer also includes pathological types such as adenocarcinoma and adenosquamous carcinoma, with cervical adenocarcinoma being estrogen-dependent. A meta-analysis showed that HRT may slightly increase the risk of tumor recurrence in patients with cervical adenocarcinoma [114].

4.1.1. Recommendation 4–1

Patients with vulvar, vaginal, and cervical squamous cell carcinoma can improve menopausal symptoms through systemic or local HRT (1a, A).

4.1.2. Recommendation 4–2

For survivors of cervical adenocarcinoma and adenosquamous carcinoma, HRT should be considered with extreme caution. If used, it requires individualized risk-benefit evaluation, reference to principles for endometrial adenocarcinoma, and close monitoring (3b, C).

4.2. Can HRT be considered for survivors of malignant tumors of the uterine body?

Endometrial cancer mostly occurs in postmenopausal women, but 25 % of patients are still premenopausal patients. In young patients, polycystic ovary syndrome (PCOS) and obesity are important risk factors [115], and most of these patients can be diagnosed early in the disease. The overall five-year survival rate of the disease is about 86 %; if the lesion is confined to the uterus, the five-year survival rate can rise to 97 % [116].

Several early retrospective studies have shown that postoperative HRT in patients with early (mainly FIGO stage IA) low-risk endometrial cancer does not increase the risk of tumor recurrence [117–120]. The results of a randomized, double-blind study of 1236 patients showed that the cancer recurrence rate of patients with early (about 91 % of stage I) endometrial cancer undergoing estrogen replacement therapy

(ERT) after surgery was 2.3 %. However, it was higher than the placebo group (1.9 %), but the recurrence rate was very low [121].

Country guidelines differ in recommendations or recommendations for whether HRT can be considered for patients with endometrial cancer after surgery. Considering that the positive impact of HRT on the quality of life of surgically menopausal patients may outweigh the risk of tumor recurrence, according to the recommendations of the NCCN and the statements of the EMAS and IGCS, this guideline recommends that systemic or topical estrogen application may be considered in patients with low-grade, early-detected endometrial cancer with low risk of recurrence. However, an individualized protocol is required, and the patient's informed consent is obtained [112]. There is no research on the application of HRT in patients with endometrial cancer of FIGO stage II and above. In addition, although estrogen-dependent tumors are related to elevated estrogen levels, they are mostly found earlier and have a better prognosis. However, non-estrogen-dependent tumors tend to be more malignant. When choosing HRT, we need to weigh the benefits and risks.

Other histological types of tumors, such as uterine sarcoma, need to decide whether to use HRT according to the expression of estrogen and progesterone receptors. Among them, endometrial stromal sarcoma often has overexpression of estrogen and progesterone receptors, and HRT is usually not recommended.

4.2.1. Recommendation 4–3

Survivors of early low-risk endometrial cancer use HRT after surgery, and their recurrence rate is very low. Individualized programs are needed, but patients' informed consent and close follow-up must be obtained (3b, C).

4.3. Can ovarian cancer survivors consider HRT?

Ovarian cancer has a poor prognosis because it is usually found late. The scope of surgery includes the removal of all visible tumor foci in the pelvic and abdominal cavity, including ovaries, uterus, omentum, and peritoneum, as well as lymph nodes or other organs. Due to the loss of ovarian function after surgery, young patients will enter menopause soon after surgery, and show menopause-related symptoms or diseases such as hot flashes, mood swings, vaginal dryness, sexual life disorders, and decreased bone mineral density, which negatively impact the quality of life. Although HRT is an effective treatment to alleviate menopausal symptoms, studies have shown that estrogen can accelerate the progression of ovarian cancer [122], and there are serious concerns and questions about the safety of postoperative HRT in patients with ovarian cancer.

There is limited evidence on the risk of cancer recurrence after HRT in patients with ovarian cancer. Among ovarian cancers, 80 % to 90 % are epithelial ovarian cancer (EOC) [123]. A randomized controlled study of 373 patients under 50 years of age with EOC, including multiple pathological types such as ovarian serous carcinoma, mucinous carcinoma, endometrioid carcinoma, and clear cell carcinoma, with an average follow-up time of 42 months, showed that HRT did not affect disease-free survival (RR = 0.90, 95 % CI: 0.52–1.54) and mortality (RR = 0.73, 95 % CI: 0.44–1.20) in patients with EOC [124]. A single-center case-control study showed no significant effect of HRT on overall survival in patients with ovarian invasive serous cystadenocarcinoma (OR = 0.90, 95 % CI: 0.24–5.08) [125]. Retrospective studies in China have shown that postoperative HRT has no adverse effect on progression-free survival and overall survival of patients with invasive EOC [126]. A meta-analysis from Cochrane showed that postoperative HRT in patients with EOC improves overall survival with little or no effect on progression-free survival. The incidence of breast cancer, transient ischemic attack, cerebrovascular accident, and myocardial infarction in HRT patients is low [127,128]. Regardless of whether estrogen and progesterone receptors in cancer tissues are positive or not, postoperative HRT has no obvious negative effect on the prognosis of ovarian cancer patients and can improve the postoperative quality of life

of patients [129]. Women experiencing severe menopausal symptoms after ovarian cancer surgery may be considered for HRT [130]. Another Meta-analysis showed that HRT may not increase the risk of tumor recurrence in patients after EOC, and the same conclusion was obtained in patients with different grades or stages of tumor [131].

It is worth noting that although some studies have suggested that postoperative HRT in patients with Low-Grade Serous Ovarian Carcinoma (LGSOC) may help prolong the progression-free survival of patients [132], considering that 80.7 % of patients have estrogen receptor expression in tumor tissues, so LGSOC is generally considered to be a hormone-responsive tumor, HRT is not currently recommended [133,134]. A prospective cohort study of 150 patients concluded that HRT did not affect the 5-year survival rate of patients with borderline ovarian tumor (BOT) [135]. According to the guidelines of the French National College of Obstetricians and Gynecologists, mucous BOT lacks hormone sensitivity, and HRT is recommended for postoperative patients under 45 years old to reduce the risk of cardiovascular disease and osteoporosis [136]. Serous BOT is aggressive and potentially hormone-sensitive, and HRT should be cautious [137,138]. Patients with germ cell tumors (except for a few types that may secrete hormones) may consider a short-term (<5 years) estrogen and progesterone combination regimen and choose topical medication whenever possible [139,140]. HRT is generally not recommended for ovarian granulosa cell tumors [139].

4.3.1. Recommendation 4–4

HRT can improve the overall survival rate of patients with epithelial ovarian cancer after surgery and improve the quality of life of patients with advanced-stage epithelial ovarian cancer. Clinicians can consider recommending individualized HRT regimens according to the condition, pathological type, stage, grade, and hormone sensitivity of the tumor (2b, B).

4.4. Can HRT be considered for patients with endometriosis?

Endometriosis is characterized by the presence of ectopic endometrial tissue, which may lead to symptoms such as dysmenorrhea and chronic pelvic pain. Some patients may require bilateral ovariectomy with or without hysterectomy to control symptoms. Surgical treatment can relieve the symptoms of endometriosis, but it also causes the decline of ovarian function, even iatrogenic POI and fertility loss. It has been controversial whether patients with endometriosis can use hormone replacement therapy after surgery. Whether estrogen can cause recurrence, spread, or canceration of residual endometriosis in the pelvic cavity is the focus of attention.

Cochrane's study shows that tibolone or a continuous combination regimen (e.g., estradiol/drospirenone tablets, estradiol dydrogesterone tablets 0.5 mg/2.5 mg) may be a safe option for postoperative hormone therapy in patients with endometriosis [141–143]. In addition, studies have shown that postoperative delayed HRT does not reduce the risk of postoperative recurrence of endometriosis [144]. Although there is no high-quality evidence at present [143], due to the low probability of disease recurrence caused by HRT after endometriosis surgery, considering the impact of early menopausal age on women's long-term health, it is still recommended that patients with endometriosis choose individualized treatment plans according to the severity of the disease after surgery [145].

4.4.1. Recommendation 4–5

Patients with iatrogenic POI because of endometriosis need to choose an individualized HRT regimen according to the severity of the disease. It is recommended that the continuous or similar combination regimen be the first choice (3b, C).

4.5. Can HRT be considered after ovariectomy for carriers of BRCA mutations?

The risk of breast cancer in women is related to age, genetics, environment, reproduction, lifestyle, and other factors [146]. Although genetic mutations account for less than 10 % of the many causes of breast cancer, BSO can reduce the risk of breast cancer by 46 % and the risk of ovarian cancer by 72 % in carriers of BRCA mutations. Therefore, according to NCCN estimates, about 65 % of BRCA mutation carriers will choose to undergo BSO before natural menopause, and more than half of BRCA1 mutation carriers will face iatrogenic POI [147].

Women under 50 years old, especially those under 46 years old, who undergo BSO, should consider initiating HRT as early as possible after surgery to reduce related diseases or symptoms caused by estrogen deficiency. A multicenter prospective study in 17 countries, including 872 BRCA1 mutation carriers who underwent BSO, showed that ERT showed protection against breast cancer in postoperative patients under 45 years of age without a history of breast cancer (HR = 0.24, 95 % CI: 0.06–0.98 after more than 5 years of medication), while progesterone was a risk factor (HR = 3.38, 95 % CI: 1.17–9.73 within 5 years of medication) [148]. Studies have suggested that HRT after BSO in BRCA mutation carriers is safe, at least in the short term or until age 51 [149].

4.5.1. Recommendation 4–6

BRCA mutation carriers without a history of breast cancer may consider HRT to relieve menopausal symptoms after BSO (3b, B).

4.6. Can breast cancer survivors consider HRT?

Breast cancer is the malignant tumor with the highest incidence in Chinese women, and its onset age is earlier than that in Europe and America [150]. According to statistics, nearly 60 % of female breast cancer in China are premenopausal patients [151]. The menopausal symptoms of breast cancer survivors are related to radiotherapy, chemotherapy, and anti-estrogen endocrine therapy. Results from RCT show that HRT increases the risk of tumor recurrence in breast cancer survivors [152–156]. A randomized, double-blind, multicenter study of 3098 breast cancer survivors showed that tibolone might not increase the risk of breast cancer recurrence in estrogen receptor-negative patients [157,158]. However, considering that the recurrence of breast cancer is related to many factors, such as age, heredity, pathological type, whether the uterus has been removed, etc., and whether HRT can be used in hormone receptor-negative patients, such patients should be individualized. Furthermore, topical estrogen application in breast cancer survivors with genitourinary tract syndrome does not increase the risk of breast cancer recurrence [159].

4.6.1. Recommendation 4–7

Breast cancer survivors usually do not recommend HRT, and patients with genitourinary tract syndrome may consider topical application of estrogen to improve symptoms (3b, B).

Contributors

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Declaration of competing interest

All members of the expert group declare that they have no competing interest.

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