The role of levonorgestrel-releasing intrauterine system for endometrial protection in women with breast cancer taking tamoxifen

Qingquan Shi[1], Jinhong Li[2], Ming Li[1], Jing Wu[1], Qiang Yao[1], Aiyun Xing[1]

[1] Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu
[2] Department of Urology, West China Hospital, Sichuan University, Chengdu (China)

Summary

Purpose of Investigation: To review the evidence concerning the efficacy of levonorgestrel-releasing intrauterine system (LNG-IUS) in preventing endometrial pathology in women treated with tamoxifen. *Materials and Methods:* Randomized controlled trials (RCTs) of women with breast cancer on tamoxifen that compared endometrial surveillance or placebo alone vs. the LNG-IUS were reviewed. The eligible trials were identified from the following electronic databases: Cochrane CENTRAL, Medline, and EMBASE. The authors extracted data on all reported outcomes and conducted meta-analyses on the endometrial polyps, endometrial hyperplasia, proliferative endometrium, and endometrium thickness. *Results:* According to the subgroup analysis, a significant reduction of endometrial polyps was obtained (OR=0.22, 95% CI 0.13-0.37, $p < 0.00001$). The use of LNG-IUS reduced the incidence of endometrial hyperplasia (OR=0.13, 95% CI 0.03-0.58, $p = 0.007$) Increased abnormal vaginal bleeding for LNG-IUS users may be an adverse aspect of LNG-IUS. *Conclusion:* This meta-analysis confirms that endometrial hyperplasia is also reduced as well as endometrial polyp formation reduced after long-term follow-up.

Key words: Levonorgestrel-releasing intrauterine system (LNG-IUS); Endometrial neoplasm; Endometrial hyperplasia; Endometrial polyps.

Introduction

Tamoxifen acting as a classical therapy for women suffering breast cancer has been proven to improve survival for those who are hormone receptor positive [1]. Five years of treatment of tamoxifen lowers the annual breast cancer death rate by 31% in women with estrogen receptor positive tumor, compared to use for one to two years [1, 2]. Its main action is as an anti-estrogen, by blocking the estrogen receptor on the breast cancer cells, thus reducing proliferation [3]. However, corresponding to the anti-estrogen tumor-suppressive action in the breast, tamoxifen has an estrogen-agonist effect and thereby different actions in different organs [4, 5]. It acts as a pure estrogen in the skeleton and endometrium but as an anti-estrogen in the vagina and bladder [3]. Although tamoxifen also reduced the risk of osteoporotic fractures, it increased the risk of endometrial cancer, and other undesirable side effects [6]. Recently, tamoxifen exposure was found to be associated with an overexpression of b-catenin oncoprotein, which may play a major role in the pathogenesis of endometrial adenocarcinoma [7]. As a result of this, the effect of tamoxifen on endometrium challenges its safety [8]. The most common endometrial changes include endometrial polyps and hyperplasia in untreated women. The risk for the endometrial carcinoma was 1.3–7.5-fold risk compared to untreated women [9]. Compared with tamoxifen, the third-generation aromatase inhibitors bringing fewer adverse effects are now part of the standard adjuvant treatment for postmenopausal women with breast cancer [10-13]. However, tamoxifen remains part of the standard adjuvant endocrine therapy for premenopausal and postmenopausal breast cancer patients, owing to the new uncertain adverse effects and the cost.

The only levonorgestrel-releasing intrauterine system (LNG-IUS) approved for general public use is a T-shaped plastic intrauterine device that releases levonorgestrel (20 ug per day) directly into the uterine cavity. It produces a very high local concentration in the endometrial tissues with low plasma concentrations gained systemically [14], lowering the potential systemic adverse effects [15]. LNG-IUS is approved for endometrial protection in women who are receiving estrogen replacement therapy [16], and it was shown to induce regression of endometrial hyperplasia [17]. In the UK in 2005, the LNG-IUS was licensed for endometrial protection for women using estrogen replacement therapy (ERT) who retained their uterus, although it is not licensed for this indication in the USA or Canada [18] .Additionally, because LNG-IUS causes gland atrophy as well as abundant impediment and decidualisation of the endometrium, it has been suggested that LNG-IUS may be effective in keeping from proliferative endometrial pathology in tamoxifen users [19]. However, the effects and safety of LNG-IUS for this are not clearly known, especially for a long-term (> one year) use.

The purpose of the present study and systematic review was therefore to assess the efficacy of the LNG-IUS in pre-

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Table 1. — *Summary of comparative, randomized, controlled trials using the levonorgestrel-releasing intrauterine system (LNG-IUS) to prevent endometrial pathology in tamoxifen.*

Trials	Designs	Menopausal state	Participants Total	Intervention	Control	Follow-up (months)	JADAD SCORE	Outcome measures
Wong *et al.* [27]	RCT	Pre and post	129	64	65	60	5	Recurrence of breast cancer, breast cancer–related deaths, endometrial polyps, endometrial hyperplasia.
Gardner *et al.* [26]	RCT	Post	122	64	58	60	5	Benign polyp, insufficient for diagnosis, atrophic or inactive, weakly proliferative or secretory, hyperplasia (no atypia), endometritis, decidualised endometrium.
Kesim *et al.* [28]	RCT	Post	142	70	72	36	5	Atrophic endometrium, insufficient material, proliferative or secretory endometrium, pseudodecidual reaction, endometrial polyp, endometrial hyperplasia without atypia.
Chan *et al.* [25]	RCT	Pre and post	129	64	65	12	5	Polyps, submucosal fibroids, normal cavity; insufficient for diagnosis, atrophic or inactive, proliferative or secretory, benign.
Gardner *et al.* [24]	RCT	Post	122	64	58	12	5	Polyps developed, submucous fibroids, histology of endometrial samples, insufficient for diagnosis, atrophic or inactive, weakly proliferative or secretory, hyperplasia (no atypia), endometritis, decidualised endometrium.

RCT = Randomized controlled trial, Pre = premenopausal; post = postmenopausal.

venting the development of endometrial hyperplasia, polyps, and carcinoma in pre- and postmenopausal women taking tamoxifen.

This systematic review analyzes the current evidence for the use of the LNG-IUS in women using tamoxifen .To determine whether long-term LNG-IUS use prevents development of endometrial pathology like hyperplasia, polyps, and endometrial adenocarcinoma in those taking adjuvant tamoxifen.

Materials and Methods

A comprehensive database search was carried out independently by Q. Shi and J. Li. The authors searched the following database: Cochrane Central Register of Controlled Trials (CENTRAL), Medline (via OVID), and EMBASE. Each Randomized controlled trial (RCT) was scored for quality to assess validity using the Jadad scoring system, which is used to evaluate studies based on randomization, blinding, and description of withdrawals and dropouts. If the Jadad score of a study was more than 3, it was considered a high-quality study [20-22]. There was no restriction on the language of the publication. The following search terms were used to identify any relevant studies: "levonorgestrel or intrauterine device or IUD or intrauterine system" and "breast neoplasm or breast cancer" and "tamoxifen" and "endometrium neoplasm or endometrium hyperplasia" and "randomized controlled trial". Two investigators evaluated all the potentially eligible studies independently without prior consideration of the result and assess the methodological quality separately.

The following criteria were used for study selection: (1) the study was a randomized controlled trial (RCT); (2) the patient was diagnosed women with breast cancer on adjuvant tamoxifen; (3) the treatment intervention was LNG-IUS vs. endometrial surveillance or placebo alone; (4) objective and/or subject outcome measures were clearly defined. Studies were excluded if: (1) the studies were not RCTs; (2) studies that examined the use of LNG-IUS in the treatment of early invasive endometrial cancers; (3) studies comparing different doses of intrauterine levonorgestrel in reduction of endometrial cancer risk without a control group.

The primary outcome measure was incidence of endometrial pathology including polyps, hyperplasia, or adenocarcinoma diagnosed at hysteroscopy with endometrial biopsy. Secondary outcome included endometrial proliferative activity, complications of the LNG-IUS including uterine perforation or pelvic infection or abnormal uterine bleeding and adverse events.

Data extraction was undertaken independently by two reviewers and then cross-checked. Any disagreements that could not be reconciled by discussion were considered by a third person. Included trial data were processed as described in the Cochrane Reviewers' handbook [23]. Statistical analyses were conducted by Review Manager 5.1.χ2 tests and I2 tests were used to assess heterogeneity in study results. If χ^2 heterogeneity was reported as $p > 0.10$ and I2 $\leq$ 50 %, heterogeneity was low. A fixed effect was used for calculations in the absence of evidence of heterogeneity; otherwise, a random effects model was applied. The authors reported odds ratios (OR) for dichotomous data and weighted mean differences (WMD) for continuous data, accompanied by 95 % confidence intervals (CI). A p value < 0.05 was considered statistically significant.

Results

The present search identified 147 reports, of which 134 were excluded on the basis of title or abstract due to irrelevant to the topic and eight were excluded from the remaining 13 literatures after we finished the reading of full

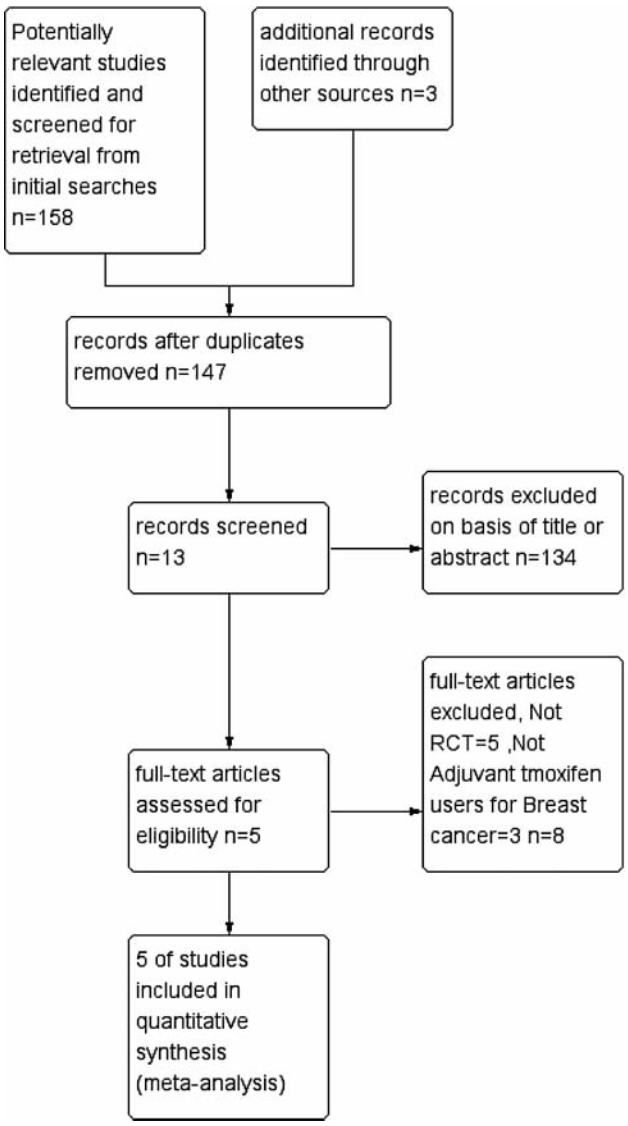

Figure 1. — Study flow diagram.

text (Figure 1). Therefore, data from a total of five studies were included in this systematic review. Table 1 shows the characteristics of the included studies. Overall, 393 women were randomized to insert LNG-IUS (n = 198) or endometrial surveillance alone (n = 195).

The combined search strategies identified five studies that met the inclusion criteria. However, the five included papers actually are three trials, two of which were five-year study and the two studies both reported 12-month and 60-month outcome, respectively [24-27]. The three randomized controlled trials, 393 women included, investigated the use of the LNG-IUS in women using tamoxifen 20 mg per 24 hours compared to surveillance alone. Chan *et al.* [25] compared endometrial surveillance alone vs. prophylactic LNG-IUS insertion before tamoxifen administration in pre- and postmenopausal women. These women suffering breast cancer required adjuvant tamoxifen after the completion of postoperative radiotherapy and chemotherapy. Wong *et al.* [27] report the final 60-month results of described Chan's trial [25]. Gardner *et al.* studies [24, 26] and Kesiml *et al.* study [28] also compared endometrial surveillance alone versus endometrial surveillance before and after insertion of LNG-IUS for 12, 60, and 36 months in postmenopausal women taking adjuvant tamoxifen treatment for at least one year, respectively. Among the above studies, no endometrium cancers or cases of hyperplasia, fewer polyps were seen in the LNG-IUS groups at both 12-month and long-term follow-up.

In this meta-analysis, two studies reported the 12-month follow-up after LNG-IUS insertion in the breast cancer patients taking adjuvant tamoxifen; heterogeneity among them is not applicable, as no endometrial hyperplasia was observed in Chan *et al.* study [25]. The fixed effects model was used, the result showed that there was no significant difference between the LNG-IUS insertion group and the surveillance alone group (OR = 0.12, 95% CI: 0.00, 6.18; p = 0.29, Figure 2). Additionally, compared to control group, 12-month use of LNG-IUS reduced the incidence of endometrial polyps (OR = 0.21, 95% CI: 0.07, 0.58; p = 0.003, Figure 3) and endometrial proliferation (OR = 0.12, 95% CI: 0.04, 0.35; $p < 0.0001$, Figure 4).

Three studies reported the long-term follow-up (>36 months) after LNG-IUS insertion in the breast cancer patients taking adjuvant tamoxifen, no heterogeneity was found among them (p = 1.0, I2 = 0%), the fixed effects model was used, the result suggested a significant reduction in the incidence of endometrial hyperplasia in the LNG-IUS users group compared to endometrial surveillance alone (OR = 0.13, 95% CI: 0.03, 0.66; p = 0.01) (Figure 2). Moreover, a significant reduction in the incidence of endometrial polyps (OR = 0.23, 95% CI: 0.13, 0.41; $p <$ 0.00001, Figure 3) and proliferative endometrium (OR = 0.15, 95% CI: 0.08, 0.30; $p < 0.00001$, Figure 4) in the LNG-IUS users group compared to endometrial surveillance alone. According to the subgroup analysis, the use of LNG-IUS reduced the incidence of endometrial hyperplasia (OR=0.13, 95% CI 0.03-0.58; p = 0.007, Figure 2), endometrial polyps (OR=0.22, 95% CI 0.13-0.37; $p <$ 0.00001, Figure 3) and endometrial proliferation (OR=0.14; 95% CI 0.08 – 0.25; $p < 0.00001$, Figure 4).

There was no statistical significance between sonographic endometrial thickness in the treatment and control groups during both short-term (MD = - 0.88 95% CI: - 1.85, 0.09; p = 0.08, Figure 5) and long-term follow-up in the selected studies (MD = - 0.15 95% CI:-0.84 0.54; p = 0.67, Figure 5). Overall, a majority of women with LNG-IUS complained of abnormal vaginal bleeding or spotting at six months compared with the control groups .However, by 12 months, this difference did not reach significance in any of the studies. After 60-month follow-up, Wong *et al.* [27]

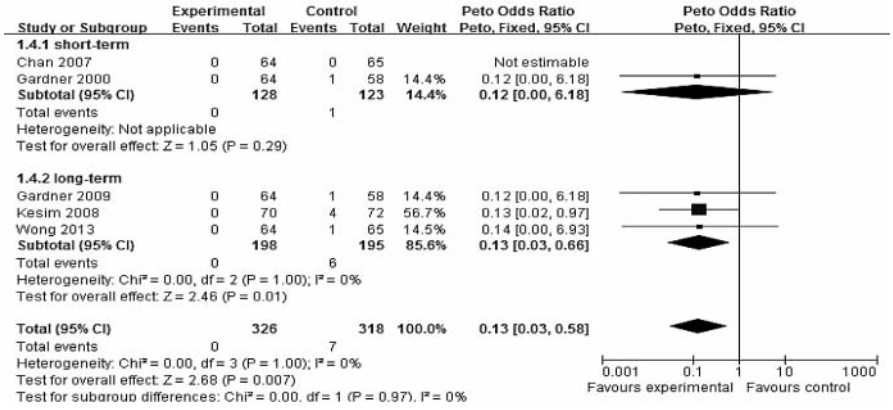

Figure 2. — Forest plot of pooled odds ratios in endometrial hyperplasia in women using the levonorgestrel-releasing intrauterine system (LNG-IUS) and tamoxifen compared to tamoxifen alone.

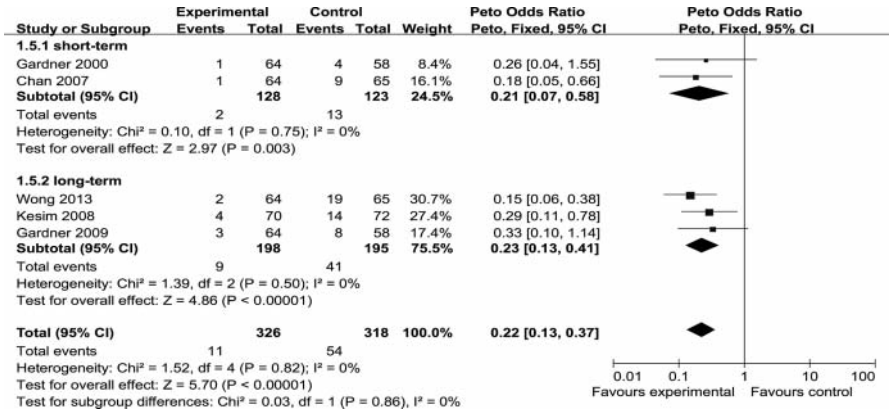

Figure 3. — Forest plot of pooled odds ratios in endometrial polyps formation in women using the levonorgestrel-releasing intrauterine system (LNG-IUS) and tamoxifen compared to tamoxifen alone.

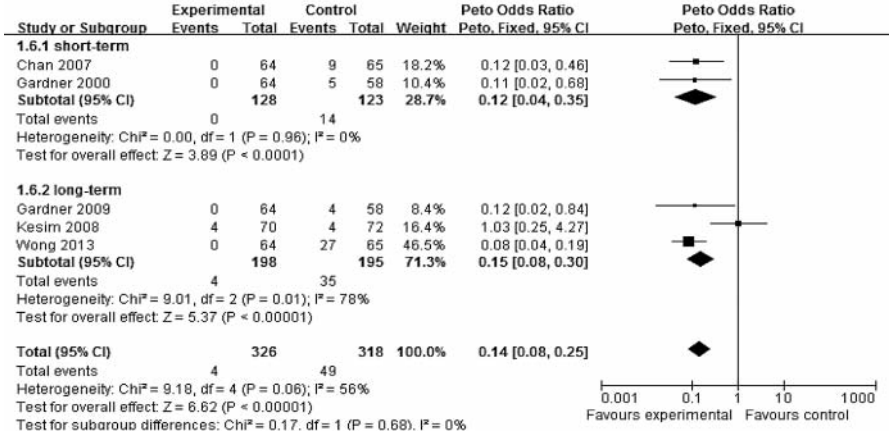

Figure 4. — Forest plot of pooled odds ratios in endometrial proliferation in women using the levonorgestrel-releasing intrauterine system (LNG-IUS) and tamoxifen compared to tamoxifen alone.

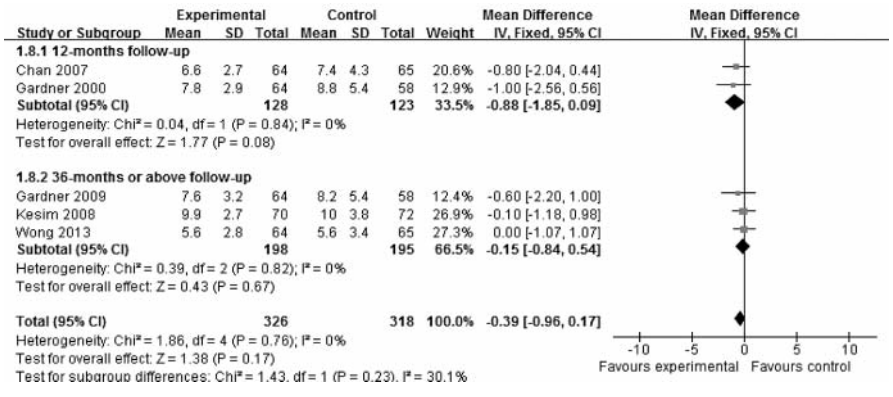

Figure 5. — Forest plot of pooled mean difference of endometrium thickness in women using the levonorgestrel-releasing intrauterine system (LNG-IUS) and tamoxifen compared to tamoxifen alone.

identified a statistically significant increase in abnormal vaginal bleeding for LNG-IUS users ($p < 0.001$), which may be an adverse aspect of LNG-IUS. Chan *et al.* [25] reported other adverse effect of LNG-IUS such as breast tenderness and acne: four women in the treatment group and two in the control group reported breast tenderness. Only one woman in the treatment group complained of mild acne during the study.

Discussion

Breast cancer is the most frequent cancer among women with a lifetime risk of up to 12% and a lifetime risk of death of up to 5% [29], while tamoxifen administration for adjuvant treatment made a significant decline of incidence of the estrogen receptor–positive breast cancer, resulting for its wide use to treat breast cancer [8]. A meta-analysis summary of 28 randomized clinical studies indicated a significant reduction (16%) in mortality [30]. Regardless of its proven effectiveness, tamoxifen is still in connection with series of adverse effects: increased incidence of abnormal bleeding, polyps, hyperplasia, and cancer, the most serious risk [31]. To those women taking tamoxifen, the longer time one uses it, the higher risk of endometrial carcinoma she suffers. As reported, the risk doubled after two years of treatment, and quadrupled after five years of use. [32-34]. However, for breast cancer patients, the benefit of tamoxifen still outweighs its risk [27].

The LNG-IUS, which delivers the progestin levonorgestrel (LNG) into the uterine cavity at a steady rate of 20 ug per day, leads to abundant regression and decidualisation of the endometrium with atrophic gland [14]. As a result of its abundant anti-proliferative effect, the LNG-IUS is deemed to lower the risk of endometrial hyperplasia and carcinoma, and perhaps be efficacious in treating hyperplasia.

In the present review, three randomized controlled trials explored endometrial protection of LNG-IUS for breast cancer women taking tamoxifen. All studies address that LNG-IUS users got a statistically significant reduction in endometrial polyps. Nevertheless, only one trial concluded that LNG-IUS could lower the risk of endometrial hyperplasia for tamoxifen users. The rest two trials considered that protection of endometrium uncertain. Also, the trials differ in inclusion criteria, design, and the outcome measures. Gardner *et al.* [24, 26] inserted LNG-IUS in postmenopausal breast cancer women who had already been taking tamoxifen for one year and then had a five-year follow-up. Wong *et al. and* Chan *et al.* [25, 27] implanted LNG-IUS in mastocarcincma patients before using tamoxifen, and also had 60-month following. Both studies [24-27] had 12-month results and 60-month conclusion. Kesiml *et al.* [28] put LNG-IUS in postmenopausal mastocarcincma women who had taken tamoxifen at least for one year and then had a 36-month follow-up. All studies used hysteroscopy and endometrial biopsy to diagnose endometrial lesion.

The primary outcome for Gardner *et al.* [24] and Chan *et al.* [25] study was endometrial pathology at first year and for Gardner *et al.* [26], Wong *et al.* [27] studies were endometrial pathology at fifth year, and for Kesim *et al.* [28] study was endometrial pathology at 36th month. All trials excluded the patients diagnosed endometrial lesion before randomization. Any endometrial pathology detected at baseline was treated. Subsequent hysteroscopy and endometrial biopsy was performed at 12, 24, 36, 48, and 60 months.

In Gardner *et al.* trial, the authors analyzed the data by received therapy, making a significant reduction in endometrial polyps in LNG-IUS users. In the entry baseline of participants, there was one case of complex hyperplasia without atypia in the control group. However, the authors fail to achieve any difference in endometrial hyperplasia between experimental group and control group. The study reported vaginal bleeding, the only significant adverse effect of LNG-IUS, which seems to be more common in those women inserted LNG-IUS after six months and this bleeding seems to be due to decidualised endometrium. In addition, there was no significant difference in endometrium thickness. The second trial randomized those participants to LNG-IUS insertion or surveillance alone before the commencement of tamoxifen. Chan *et al.* and Wong *et al.* made a statistically significant reduction concerning polyps in treatment group at 12th month ($p = 0.002$) and at 60th month ($p < 0.001$) [25, 27]. No endometrial hyperplasia or carcinoma was found in either group. Unscheduled vaginal bleeding was not significantly different from the control group at one year. However, at fifth year, Wong *et al.* found a significant increase in abnormal bleeding for LNG-IUS users ($p < 0.001$) [27]. Other adverse effects like breast tenderness and mild acne were uncommonly reported, suggesting its good acceptance. Similarly, the trial did not find a significant difference in endometrial thickness between LNG-IUS users and control group. Furthermore, the authors showed an uncertainty of LNG-IUS, the risk of breast cancer recurrence as a result of mammary cell proliferation. The third trial [28] randomized participants to the LNG-IUS or no treatment after taking tamoxifen for at least one year. There was also no significant difference between those taking or not taking tamoxifen, as local progestogen affected the stroma. The incidences of endometrial polyps (19%) and endometrial hyperplasia (5.5%) in the control group after 36 months compared to only 5.7% and 0%, respectively, in the LNG-IUS group [28]. Spotting, the most common form of vaginal bleeding, in LNG-IUS users was only observed at first year. Headache and mastalgia were observed both in control (7.8%) and treatment group (12%). This review extends the findings of the recent Cochrane systematic review investigating the efficacy of LNG-IUS in women taking ta-

moxifen [20] by including one further randomized controlled trial [28] and the long-term follow-up data from the RCT by Gardner *et al.* [26] and Wong *et al.*[27]. This meta-analysis confirms that endometrial hyperplasia is also reduced as well as endometrial polyp formation reduced after long-term follow-up. Additionally, compared to Wan and Holland [17], the present authors add one latest study [27] which was a 60-month follow-up for inserting LNG-IUS prophylactically in breast cancer patients before taking tamoxifen. However, meta-analysis regarding development of hyperplasia was limited because of the relative rarity of the event and thus the odds ratio calculation was weighted heavily towards a single study. In the trials reviewed here, in the Cochrane review [19] and in Wan and Holland review [17], the risk of bias is low but none of the trials were adequately powered to make a significant difference in the occurrence of cancer. The effect of LNG-IUS in reducing the incidence of cancer in these women is therefore unknown.

All of the included studies were RCTs and the qualities of these RCTs were assessed by Jadad scoring system. Despite a thorough search strategy, unpublished studies may have been missed leading to publication bias. Funnel plots examining the existence of bias are not meaningful due to the small number of studies in subgroup analysis. In this review, the three trials of women using LNG-IUS in conjunction with tamoxifen showed no statistical evidence of significant heterogeneity in the endometrial outcomes.

Conclusion

Based on the data available, the meta-analysis confirms that not only is endometrial polyp formation reduced at long-term follow-up but endometrial hyperplasia is also reduced. This is clinically significant, as endometrial hyperplasia of varying degrees confers increased risk of cancer. Whether LNG-IUS protects against or reduces the risk of endometrial cancer for women on tamoxifen following breast cancer remains uncertain. Because of its uncertainty of breast cancer recurrence, larger studies are still necessary.

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Address reprint requests to:
AIYUN XING, M.D.
Department of Obstetrics and Gynecology
West China Second University Hospital,
Sichuan University, 20# Renminnan Road,
Chengdu, Sichuan 610041 (China)
e-mail: aiyunx2013@163.com