Examining the effect of Kuntai capsule combined with HRT in the treatment of premature ovarian insufficiency: A systematic review and meta-analysis

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Abstract. While Chinese herbal medicines have been used to treat premature ovarian insufficiency (POI), their efficacy is currently unclear. The present study aimed to review and evaluate the efficacy of the Kuntai capsule combined with hormone replacement therapy (HRT) in treating POI. The China National Knowledge Infrastructure, WanFang, Chinese Biomedical Literature, PubMed, Embase and Cochrane Library databases were searched from the inception of the database to 25th October 2020, for studies comparing the therapeutic effect of Kuntai capsule combined with HRT vs. HRT alone in women with POI. The Cochrane Risk of Bias assessment tool was used to assess the quality of the studies, and the results were reported as weighted mean differences (MD) with 95% confidence intervals (CI). The present study included 10 trials involving 742 women with POI. When compared with HRT alone, HRT combined with Kuntai capsule significantly increased the number of antral follicles (AFC) (MD=0.88; 95% CI, 0.48-1.29; P<0.00001), anti-Müllerian hormone (AMH) levels (MD=0.24, 95% CI, 0.13 to 0.35, P<0.00001) and significantly improved peri-menopausal symptoms [MD=-2.26; 95% CI, -3.77-(-0.75); P=0.003]. The combined treatment regimen significantly decreased the levels of follicle-stimulating hormone [MD=-5.60; 95% CI, -7.98-(-3.22); P<0.00001] and luteinizing hormone [MD=-2.42; 95% CI, -3.40-(-1.44), P<0.00001] and significantly increased the level of estradiol (MD=13.94; 95% CI, 4.16-23.71; P<0.00001). Therefore, the Kuntai capsule combined with HRT could potentially be used as a supplementary therapy to alleviate menstrual disorders and peri-menopausal symptoms and improve serum sex hormone levels in women with POI. The observed increase in the number of AFC in patients with POI treated with the combined therapy was indicative of improved ovarian reserve function. Therefore, combining the Kuntai capsule and HRT had am improved curative effect for POI treatment compared with HRT alone. However, as the present study was limited by the quality of the included reports, additional high-quality studies with extensive sample sizes are required to verify the findings.

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Key words: Kuntai capsule, premature ovarian insufficiency, number of antral follicles

Introduction

Premature ovarian insufficiency (POI) is an ovarian dysfunction that mainly occurs in women aged <40 years (1) and is characterized by menstruation abnormalities, elevated levels of follicle-stimulating hormone (FSH) and fluctuating estrogen hormone levels (2). The final stage of POI, premature ovarian failure, is associated with different degrees of perimenopausal symptoms, such as mood changes, hot flashes and trouble sleeping (3,4). POI affects ~1% of women worldwide (3) and, if not treated, may cause several long-term health conditions, such as osteoporosis, cardiovascular disease, anxiety and depression (4,5).

Presently, a standard treatment for POI is estrogen/progesterone combination therapy. However, this hormone replacement therapy (HRT) is associated with increased health risks, including breast cancer, stroke and cardiovascular diseases (5). According to Traditional Chinese Medicine, ovarian reserve hypofunction and infertility are caused by various conditions, such as kidney malfunction. Therefore, in Traditional Chinese Medicine, ovarian reserve hypofunction and infertility can be treated with alternative therapies (6).

Previous research has demonstrated certain therapeutic effects of the Kuntai capsule on certain symptoms associated with POI, which are related to decreased hormone levels (7). The Kuntai capsule has been used as a Chinese patent medicine for low ovarian reserve. The capsule is based on Huanglian Ejiao decoction consisting of six Chinese medicines: Coptis, Ejiao, *Rehmannia glutinosa*, *Scutellaria baicalensis* Georgi, *Poria cocos* and white peony root, which has been previously reported to improve peri-menopausal and menopausal symptoms (8). A meta-analysis found that in patients with POI,

HRT combined with the Kuntai capsule is associated with a higher number of basal antral follicles, an increased number of eggs and a reduced cycle cancellation rate (9). Another 1-year study reported that adding the Kuntai capsule to conventional HRT improved the pregnancy rate in patients with POI (10). However, this regimen was associated with some adverse reactions (10).

The present study aimed to critically analyze the existing randomized clinical trials (RCTs) on the efficiency of the Kuntai capsule for POI treatment and assess whether the Kuntai capsule combined with HRT was more effective compared with HRT alone. These results may provide an evidence-based evaluation of the Kuntai capsule's efficacy for the treatment of POI.

Materials and methods

Data sources and search strategy. A systematic literature search of the China National Knowledge Infrastructure (https://www.cnki.net), WanFang (https://med.wanfangdata.com.cn/), Chinese Biomedical Literature PubMed (https://www.sinomed.ac.cn/index.jsp) (https://pubmed.ncbi.nlm.nih.gov), Embase (http://embase.com) and Cochrane Library databases (https://www.cochranelibrary.com/central/about-central) was performed from the inception of the databases to 25th October 2020. RCTs that reported using the Kuntai Capsule treatment for POI and were written in English or Chinese were included. The following keywords were used: 'Kuntai capsule' AND ('premature ovarian insufficiency' OR 'decline in ovarian reserve' OR 'ovarian reserve dysfunction' OR 'low ovarian reserve') AND 'randomized controlled trial'. A total of two reviewers conducted the searches and both reviewers agreed on the selected studies to be included in the present manuscript. In case of differences in the selection of studies, a third author was contacted to resolve the issue.

Inclusion and exclusion criteria. The inclusion criteria used were as follows: i) RCTs; ii) POI diagnosis based on The European Society of Human Reproduction and Embryology, Guideline Group on POI (2); iii) patients aged <40 years with amenorrhea or oligomenorrhea for ≥4 months and serum follicle-stimulating hormone (FSH) levels >25 IU/l on ≥2 separate measurements (>4 weeks apart); iv) studies that reported data on the control group of patients treated with HRT alone; and v) studies that reported on outcomes of serological indices, such as levels of serum anti-Müllerian hormone (AMH), FSH, luteinizing hormone (LH), estradiol (E2), antral follicle count (AFC), Kupperman score (11) and imaging indicators, such as ovarian volume, endometrial thickness and peak systolic velocity (PSV) of the ovarian artery.

The exclusion criteria were as follows: i) Repeated published literature; ii) studies written in languages other than Chinese and English; iii) a lack of access to the full text; and iv) retrospective, cohort and qualitative studies, case reports or series, experience summaries and non-human studies.

Data extraction. The relevant data, including title, first author name, publication year, patient grouping, age, course of the disease, treatment, control group type, indicators such as AMH, AFC, Kupperman score, FSH, LH, E2, ovarian volume, endometrial thickness and PSV were independently collected by two authors.

Risk of bias. The risk of bias in the included studies was assessed using the Cochrane Risk of Bias Tool (12).

Statistical analysis. RevMan Manage (version 5.3; The Cochrane Collaboration) was used for the meta-analysis of each intervention pair (Kuntai capsule combined with HRT treatment vs. HRT alone). Treatment effectiveness was expressed as weighted mean differences (MDs) and 95% confidence intervals (CIs) for continuous outcomes. Heterogeneity was assessed using a χ^2 test and I^2 statistics. The random-effects model was used irrespective of the inter-study heterogeneity measured using the I^2 statistic. The Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines were strictly followed (13), and the requirements for ethics approval and patient consent were waived since the study used previously published data.

Results

Study selection and characteristics. Screening identified a total of 742 articles. Of these articles, 10 met the criteria for standard RCTs and were included after the layer-by-layer screening (14-23). The included studies reported data on 925 patients. Of these patients, 462 received the Kuntai capsule combined with HRT treatment and 463 were treated with HRT alone. HRT treatment protocols included fenmetone, cremon and estrogen and progesterone therapy. The A similar HRT protocol was used in both the study and control groups. All patients were treated for 3 months and the changes in outcome indices before and after the treatment were compared (Table I). The flowchart of the screening is shown in Fig. 1. The Cochrane Risk of Bias Tool assessment showed that all 10 studies described the method of random grouping but did not detail the blinding method and allocation concealment, which could have affected the quality of the research. All RCTs were identified as having a 'high' or 'unclear' risk of bias (Fig. 2).

Serum gonadotrophin and estradiol hormone levels. All 10 studies reported data on sex hormone levels. The Kuntai capsule combined with HRT treatment was associated with significantly reduced levels of FSH [MD=-5.60; 95% CI, -7.98-(-3.22); P<0.00001; I^2=97%] and LH [MD=-2.42; 95% CI, -3.40-(-1.44); P<0.00001; I^2=94%] (Figs. 3 and 4). Moreover, the Kuntai capsule, in combination with HRT treatment, significantly increased E2 levels (MD=13.94; 95% CI, 4.16-23.71; P<0.00001; I2=96%) when compared with HRT only (Fig. 5).

AMH levels. A total of six studies (14,15,18-21) assessed the AMH levels. The Kuntai capsule treatment led to significantly increased levels of AMH (MD=0.24; 95% CI, 0.13-0.35; P<0.00001; I^2=92%) (Fig. 6).

Number of AFCs. A total of five studies (14,15,19-21) assessed the numbers of AFC. The pooled results showed that the numbers of AFC were significantly greater in the combined

Table I. Features of the included studies.

First author, year	Cases (Kuntai + HRT group/HRT group), n	Age, years (Kuntai + HRT group/ HRT group; mean ± SD)	Kuntai + HRT group drug regimen	HRT group drug regimen	Outcome measured	(Refs.)
Luan *et al*, 2017	58/60	42.3±2.2/41.2±3.1	Kuntai capsule (2,000 mg three times daily) and fenmeton (one dose per day)	Fenmetone (one dose per day)	AMH, AFC and serum sex hormone levels	(14)
Li *et al*, 2014	20/20	34.2±6.9/34.0±7.2	Kuntai capsule (2,000 mg three times daily) and cremon (one dose per day)	Cremon (one dose per day)	AMH, AFC and serum sex hormones levels and imaging examination	(15)
Jia *et al*, 2019	46/46	30.2±2.1/30.4±2.1	Kuntai capsule (2,000 mg three times daily) and fenmetone (one dose per day)	Fenmetone (one dose per day)	Serum sex hormone levels	(16)
Wu *et al*, 2019	50/50	35.0±3.3/34.6±3.5	Kuntai capsule (2,000 mg three times daily) and cremon (one dose per day)	Cremon (one dose per day)	Serum sex hormone levels and Kupperman score	(17)
Yuan *et al*, 2019	40/40	34.2±2.8/34.1±3.0	Kuntai capsule (2,000 mg three times daily) and cremon (one dose per day)	Cremon (one dose per day)	AMH and serum sex hormone levels	(18)
Yuan *et al*, 2018	40/40	35.2±2.6/35.8±2.1	Kuntai capsule (2,000 mg three times daily) and cremon (one dose per day)	Cremon (one dose per day)	AMH, AFC and serum sex hormone levels	(19)
Hong *et al*, 2018	30/30	31.3±6.6/34.6±3.5	Kuntai capsule (2,000 mg three times daily) and cremon (one dose per day)	Cremon (one dose per day)	AMH, AFC and serum sex hormone levels, Kupperman score and imaging examination	(20)
Hu *et al*, 2018	100/100	40.2±1.3/38.3±2.0	Kuntai capsule (2,000 mg three times daily) and fenmetone (one dose per day)	Fenmetone (one dose per day)	AMH, AFC and serum sex hormone levels and imaging examination	(21)
Xiao *et al*, 2015	45/45	36.2±3.9/36.2±4.1	Kuntai capsule (2,000 mg three times daily) and cremon (one dose per day)	Cremon (one dose per day)	Serum sex hormone levels, Kupperman score and imaging examination	(22)
Yao *et al*, 2013	33/32	32.5±3.4/31.4±3.7	Kuntai capsule (2,000 mg three times daily) and cremon (one dose per day)	Cremon (one dose per day)	Serum sex hormone levels and Kupperman score	(23)

Femoston treatment is estradiol 2 mg and dydrogesterone 10 mg, cremon treatment is estradiol valerate 2 mg and estradiol cyproterone 10 mg. HRT, hormone replacement therapy.

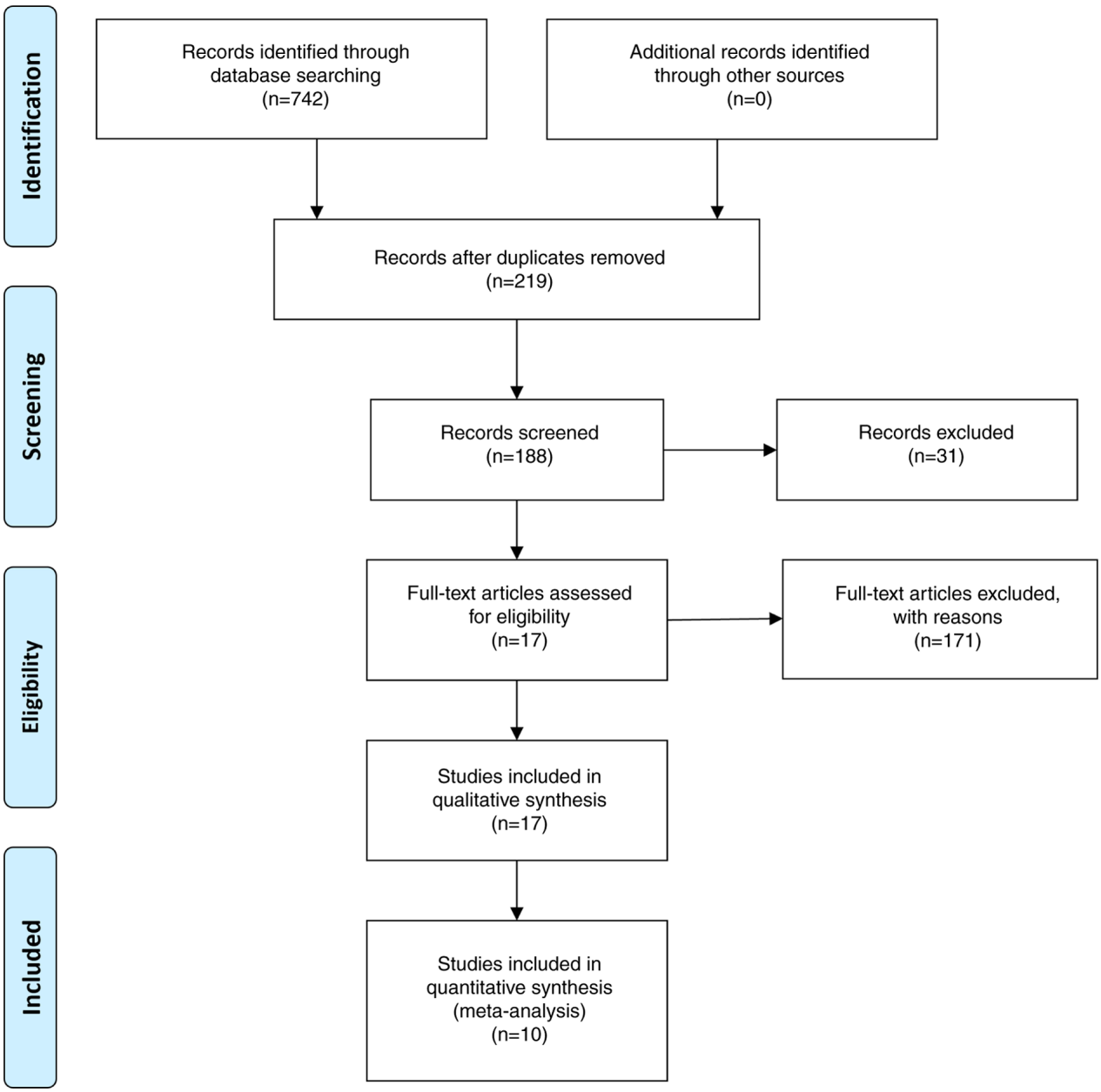

Figure 1. Flow diagram of the study selection process demonstrating number of search results obtained from databases and number of studies screened to arrive to the final number of included studies.

treatment group compared with the HRT alone group (MD=0.88; 95% CI, 0.48-1.29; P<0.00001; I^2=95%) (Fig. 7).

Improvement in perimenopausal symptoms. A total of four studies (17,20,22,23) used the Kupperman index to evaluate the improvement in perimenopausal symptoms. The pooled results suggested that the Kuntai capsule combined with HRT significantly improved the perimenopausal symptoms in patients with POI [MD=-2.26; 95% CI, -3.77(-0.75); P=0.003; I^2=67%] compared with the HRT regimen alone (Fig. 8).

Effects on the ovaries and uterus. A total of two studies (20,22) assessed ovarian volume, three (20-22) assessed endometrial thickness and one study (15) assessed PSV. The pooled analysis indicated that ovarian volumes were comparable in both groups of patients (MD=0.03; 95% CI, -0.60-0.65; P=0.94; I^2=0%) (Fig. 9). However, the Kuntai capsule combined with HRT significantly improved the endometrial thickness (MD=0.78; 95% CI, 0.26-1.31; P=0.004; I^2 =47%) (Fig. 10) and PSV (MD=1.24; 95% CI, 0.76-1.72; P<0.00001) (Fig. 11) in patients with POI.

Discussion

The present study showed that combining the Kuntai capsule and HRT treatment significantly improved AMH levels and the number of AFCs in patients with POI compared with those treated with HRT alone. Kuntai capsule treatment also significantly reduced perimenopausal symptoms, reduced FSH and LH serum levels and increased serum levels of E2. These results suggested that the Kuntai capsule and HRT combination had an improved curative effect on improving

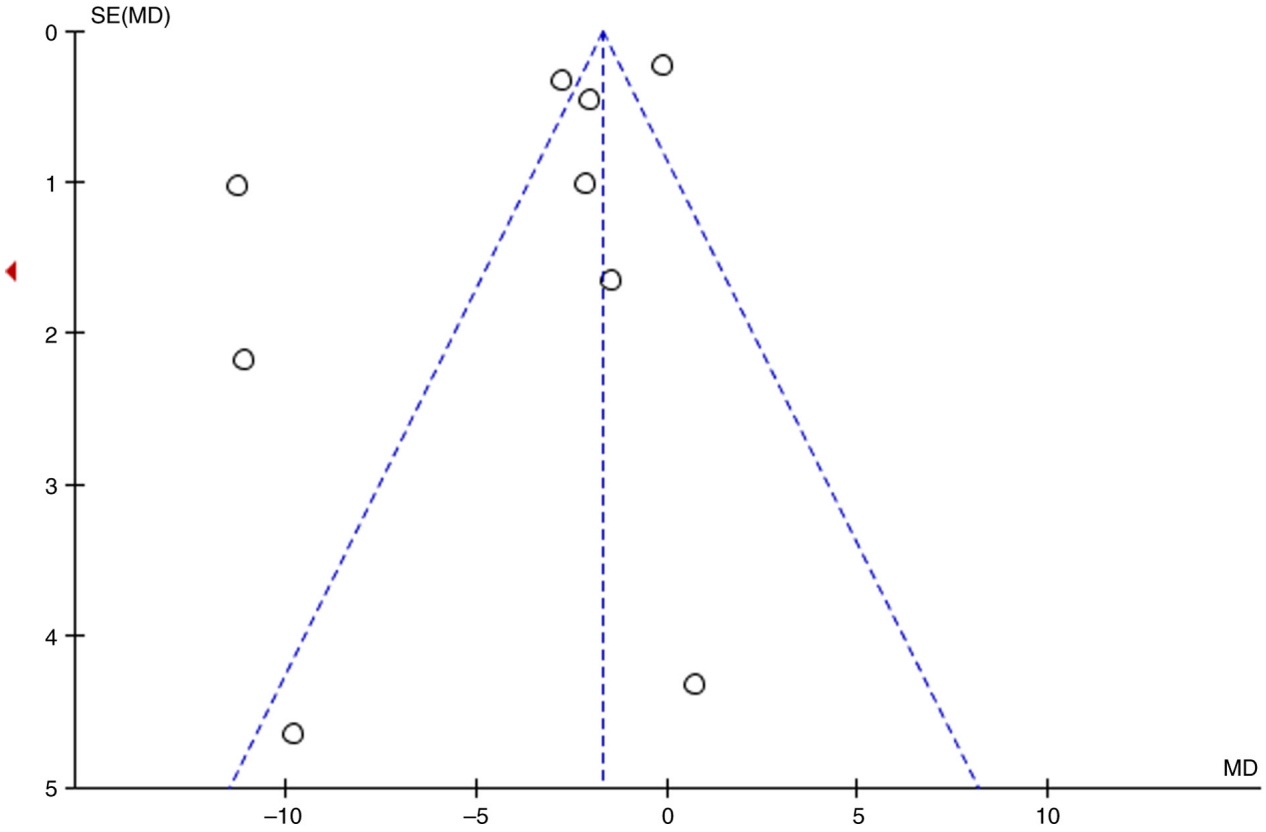

Figure 2. Risk of bias assessment in included studies. Dotted line indicates the MD and SE of the pooled analysis. MD, mean difference.

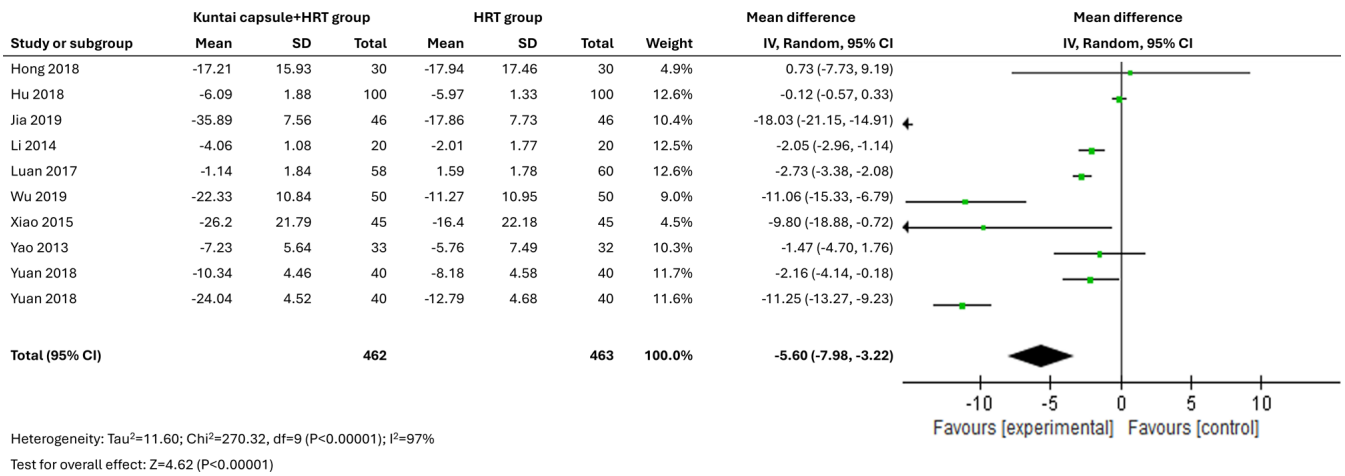

Figure 3. Analysis of serum follicle-stimulating hormone levels before and after intervention. HRT, hormone replacement therapy.

ovarian reserve function during POI treatment compared with monotherapy with HRT alone.

POI has a profound negative impact on the quality of life (24). While HRT can relieve symptoms and mitigate the impact of prolonged estrogen deficiency, it mimics the normal physiological and endocrinological status, with no evidence of improvement in ovarian function (2). Moreover, HRT increases various health risks, including the risk for breast cancer, stroke and cardiovascular diseases (5).

Several traditional medical therapies, such as acupuncture and Chinese medicine, have been reported as being effective for the treatment of POI. Pharmacological studies have reported that the Kuntai capsule inhibits the apoptosis of ovarian granulosa cells in mice with POI and improves the secretion of sex hormones, thereby improving impaired ovarian function (25). Results of an animal study showed that the Kuntai capsule activates the PI3K/AKT/mTOR signaling pathway to improve the ovarian reserve function of mice with POI and protect their fertility (26). The aforementioned studies demonstrated the potential clinical value of the Kuntai capsule for POI treatment (27). A previous systematic review reported the superior efficacy

	Kuntai capsule+HRT group			HRT group				Mean difference	Mean difference
Study or subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Hong 2018	0	0	45	0	0	45		Not estimable	
Hu 2018	-15.42	10.42	50	-15.27	10.54	50	4.6%	-0.15 (-4.26, 3.96)	
Jia 2019	-9.8	11.21	21	-10.46	10.77	25	2.1%	0.66 (-5.73, 7.05)	
Li 2014	-2.32	0.96	20	-1.51	1.01	20	21.9%	-0.81 (-1.42, -0.20)	
Luan 2017	-0.83	0.8	58	0.21	0.6	60	23.5%	-1.04 (-1.30, -0.78)	
Wu 2019	-6.33	0.52	100	-4.13	0.34	100	23.8%	-2.20 (-2.32, -2.08)	
Xiao 2015	-7.51	14.71	30	-9.75	16.15	30	1.5%	2.24 (-5.58, 10.06)	
Yao 2013	-29.1	8.39	45	-19.6	7.61	45	6.4%	-9.50 (-12.81, -6.19)	
Yuan 2018	-17.49	4.06	50	-11.13	4.17	50	14.5%	-6.36 (-7.97, -4.75)	
Yuan 2018	-7.58	10.84	19	-8.24	10.61	16	1.8%	0.66 (-6.47, 7.79)	
Total (95% CI)			**438**			**441**	**100.0%**	**-2.42 (-3.40, -1.44)**	

Heterogeneity: Tau²=1.05; Chi²=129.71, df=8 (P<0.00001); I²=94%

Test for overall effect: Z=4.85 (P<0.00001)

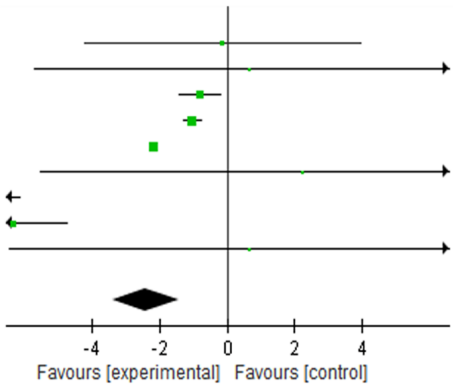

Figure 4. Analysis of serum luteinizing hormone levels before and after intervention. HRT, hormone replacement therapy.

	Kuntai capsule+HRT group			HRT group				Mean difference	Mean difference
Study or subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Hong 2018	83.22	219.01	30	61.36	147.9	30	1.0%	21.86 (-72.71, 116.43)	
Hu 2018	7.67	27.38	100	9.02	27.36	100	13.7%	-1.35 (-8.94, 6.24)	
Jia 2019	61.78	10.54	46	33.78	5.94	46	14.7%	28.00 (24.50, 31.50)	
Li 2014	-18.22	36.66	20	-9	35.53	20	8.4%	-9.22 (-31.59, 13.15)	
Luan 2017	-5.11	28.87	58	-31.44	32.82	60	12.5%	26.33 (15.19, 37.47)	
Wu 2019	47.46	20.96	50	34.7	14.82	50	13.9%	12.76 (5.64, 19.88)	
Xiao 2015	2.936	3.43	45	0.36	2.77	45	14.9%	2.58 (1.29, 3.86)	
Yao 2013	0	0	33	0	0	32		Not estimable	
Yuan 2018	136.19	81.72	40	73.22	53.07	40	6.2%	62.97 (32.77, 93.17)	
Yuan 2018	38.49	10.5	40	30.15	7.29	40	14.6%	8.34 (4.38, 12.30)	
Total (95% CI)			**462**			**463**	**100.0%**	**13.94 (4.16, 23.71)**	

Heterogeneity: Tau²=165.97; Chi²=215.97, df=8 (P<0.00001); I²=96%

Test for overall effect: Z=2.79 (P=0.005)

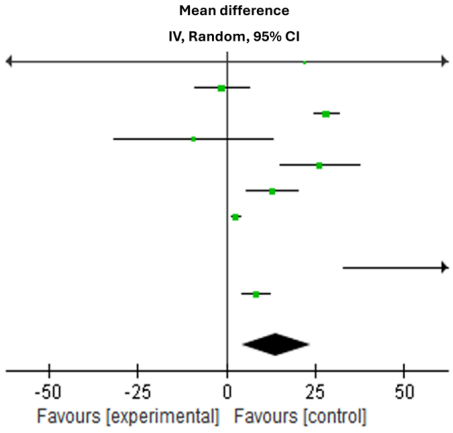

Figure 5. Analysis of serum estradiol levels before and after intervention. HRT, hormone replacement therapy.

	Kuntai capsule+HRT group			HRT group				Mean difference	Mean difference
Study or subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Hong 2018	0.05	0.48	30	0.08	0.57	30	10.4%	-0.03 (-0.30, 0.24)	
Hu 2018	0.12	0.07	1000	0.02	0.08	100	28.9%	0.10 (0.08, 0.12)	
Li 2014	1.52	0.44	20	0.76	0.53	20	8.8%	0.76 (0.46, 1.06)	
Luan 2017	0.02	0.09	58	-0.05	0.08	60	28.5%	0.07 (0.01, 0.10)	
Yuan 2018	2.06	0.7	40	0.99	0.64	40	9.1%	1.07 (0.78, 1.36)	
Yuan 2018	0.55	0.46	40	0.34	0.47	40	14.2%	0.21 (0.01, 0.41)	
Total (95% CI)			**288**			**290**	**100.0%**	**0.24 (0.13, 0.35)**	

Heterogeneity: Tau²=0.01; Chi²=65.71, df=5 (P<0.00001); I²=92%

Test for overall effect: Z=4.39 (P<0.0001)

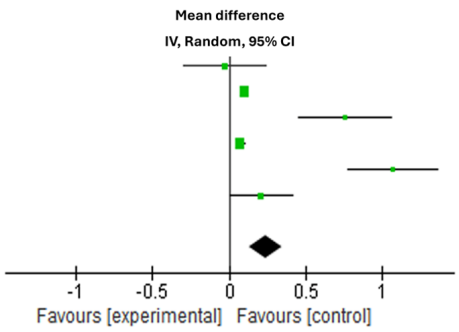

Figure 6. Analysis of serum anti-Müllerian hormone levels before and after intervention. HRT, hormone replacement therapy.

	Kuntai capsule+HRT group			HRT group				Mean difference	Mean difference
Study or subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Hong 2018	1.07	1.64	30	0.83	1.24	30	13.6%	0.24 (-0.50, 0.98)	
Hu 2018	1.24	0.3	100	0.04	0.24	100	24.1%	1.20 (1.12, 1.28)	
Li 2014	0.55	0.54	20	0	0.79	20	19.3%	0.55 (0.13, 0.97)	
Luan 2017	0.17	0.37	58	-0.43	0.29	60	23.8%	0.60 (0.48, 0.72)	
Yuan 2018	3.38	1.05	40	1.75	0.91	40	19.1%	1.63 (1.20, 2.06)	
Total (95% CI)			**248**			**250**	**100.0%**	**0.88 (0.48, 1.29)**	

Heterogeneity: Tau²=0.18; Chi²=85.64, df=4 (P<0.00001); I²=95%

Test for overall effect: Z=4.24 (P<0.0001)

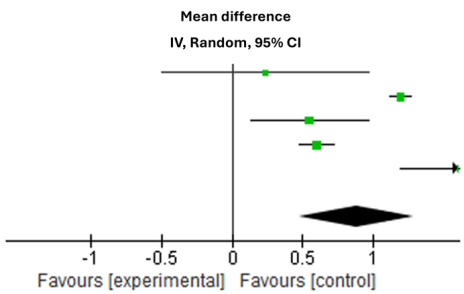

Figure 7. Analysis of antral follicle count before and after intervention. HRT, hormone replacement therapy.

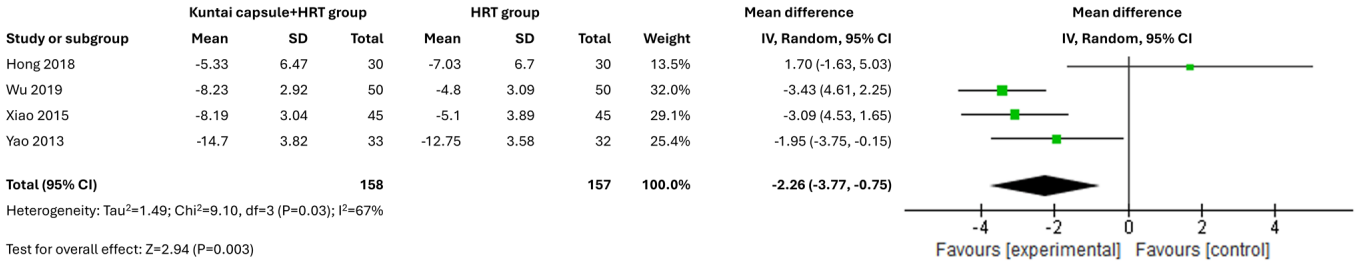

Figure 8. Analysis of Kupperman score before and after intervention.

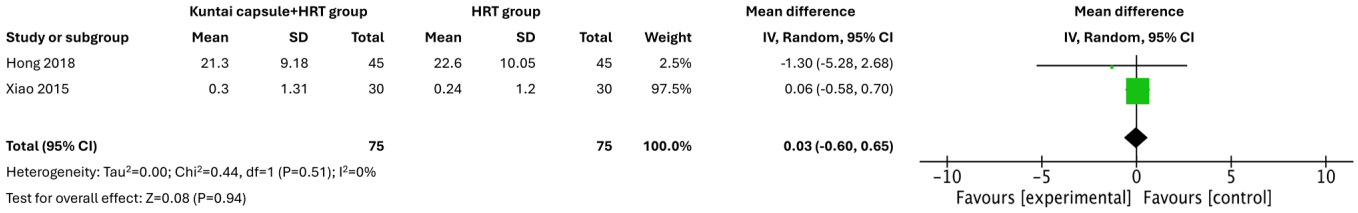

Figure 9. Analysis of ovarian volume before and after intervention. HRT, hormone replacement therapy.

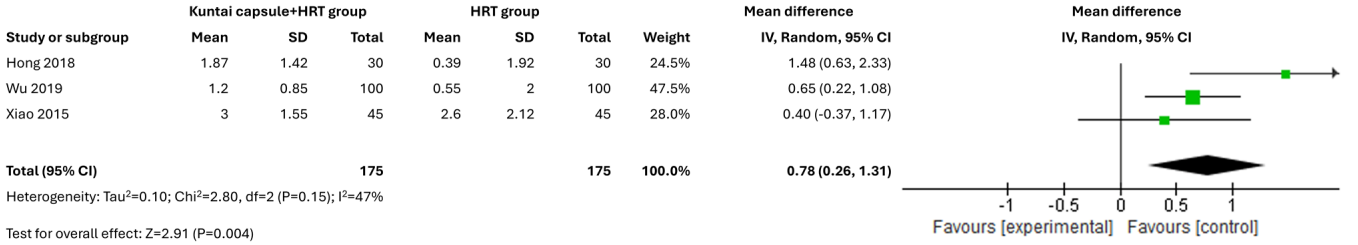

Figure 10. Analysis of endometrial thickness before and after intervention. HRT, hormone replacement therapy.

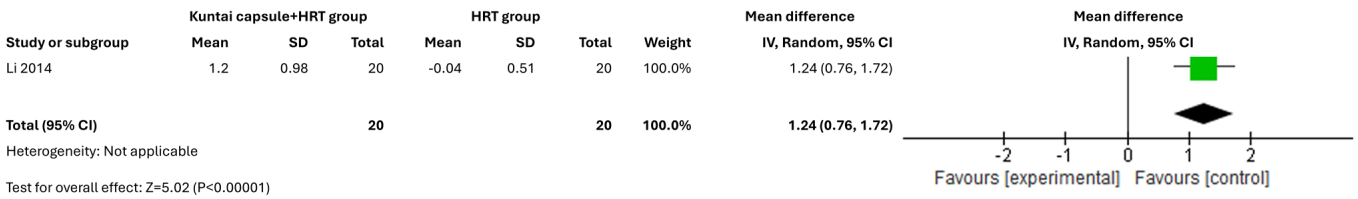

Figure 11. Analysis of peak systolic velocity before and after intervention. HRT, hormone replacement therapy.

and safety of the Kuntai capsule combined with HRT for POI treatment compared to HRT alone and showed that the Kuntai capsule combined with HRT can regulate serum estrogen and progesterone levels and reduce the adverse effects of hormone application such as nausea, vomiting, abdominal distension, headache, dysmenorrhea, breast tenderness, vaginal spotting, premenstrual syndrome and abnormal hepatic function. (28). A double-blind, randomized, controlled clinical study by Chen *et al* (29) investigated the clinical effectiveness and safety of the Kuntai capsule on peri-menopausal symptoms in patients with endometriosis who undergo postoperative gonadotropin-releasing hormone agonist (GnRH-a) treatment. The study reported that the main reported side effects of the combined Kuntai capsule and GnRH-a treatment included vaginal bleeding or spotting and breast-distending pain and showed that this regimen was associated with a significantly lower incidence of adverse effects compared with the regimen of GnRH-a + tibolone, a selective tissue-estrogenic-activity regulator.

In agreement with previous reports, the present study confirmed that the combined regimen of the Kuntai capsule with HRT effectively reduced hot flushes and related symptoms, reduced FSH and LH serum levels and increased serum levels of E2. Ma *et al* (30) showed that the Kuntai capsule was more effective in reducing the levels of FSH and LH and increasing the level of E2 compared with HRT only in the treatment of patients with premature ovarian failure. The results of the present study further confirmed these observations.

Furthermore, the present study showed that the Kuntai capsule combined with HRT increased endometrial thickness and peak systolic velocity of the ovarian artery, which indicated improved uterine and ovarian condition. It could be suggested that such changes may manifest in potentially increased pregnancy rates (28). On the other hand, combined therapy did not

significantly affect the ovarian volume, which is considered as a marker of ovarian reserve (3,4). Furthermore, a meta-analysis by Zhang *et al* (31) reported that the Kuntai capsule improved the ovulation and pregnancy rates of patients with ovulatory disorders who underwent assisted reproduction treatment.

Additionally, the present study demonstrated that the combined regimen of the Kuntai capsule and HRT significantly improved AMH levels and the number of basic antral follicles in patients with POI. A study by Lian and Jiang (32) showed that the Kuntai capsule increased the number of retrieved oocytes and improved the quality of oocytes and embryos in patients undergoing fertility treatments. The Kuntai capsule combined with routine HRT could potentially be used before ovulation induction to increase the number of oocytes and reduce the cycle cancellation rate. Future studies should focus on the potential value of the Kuntai capsule in reproductive medicine.

While there have been two previous meta-analyses (33,34) that provided evidence of the increased effectiveness of the Kuntai capsule combined with HRT vs. HRT alone in improving outcomes of POI, the present study was unique in that it used a more robust inclusion criteria to include high quality data. Firstly, only studies which diagnosed POI based on The European Society of Human Reproduction and Embryology, Guideline Group on POI were included (2). Additionally, studies with patients <40 years in age were selected, with amenorrhea or oligomenorrhea for ≥4 months and serum FSH >25 IU/l on at least two separate measurements (>4 weeks apart). This provided a more robust diagnosis of POI, thereby providing higher-quality evidence.

The present study had certain limitations. First, the 'unclear' risk of bias in most incorporated studies reduced the credibility of the conclusions. Therefore, RCTs that comply with the Consolidated Standards of Reporting Trials reporting system are required to confirm our observations (32). Second, all included studies were conducted in China and reported data exclusively on patients of Chinese origin, thus limiting the generalizability of these results. Further trials of Traditional Chinese Medicines must include diverse populations and regions to provide more accurate and reliable data. Third, only articles written in Chinese and English were included because of language restrictions. Fourth, none of the included studies reported data on adverse reactions caused by treatment with the Kuntai capsule, hence a separate meta-analysis for this could not be conducted. Finally, the present study was limited by the quality of the included literature. Additional higher-quality studies with extensive sample sizes are needed to verify these observations and provide evidence supporting the clinical use of the Kuntai capsule.

In summary, the Kuntai capsule combined with HRT treatment could alleviate menstrual disorders and peri-menopausal symptoms and reduce serum sex hormone levels in patients with POI. This treatment also significantly increased the number of antral follicles in patients with POI compared with HRT alone. However, the present study was limited by the quality of the literature included. Additional high-quality studies with extensive sample sizes are required to verify these findings. However, given the limited side-effects of Kuntai capsule and potential benefits demonstrated through the present meta-analysis, it may be considered as a future supplemental therapy in patients using HRT with POI.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FL conceived and designed the study. FL, JL and LW collected the data, performed the literature search and analyzed the data. FL was involved in the writing of the manuscript. FL edited the manuscript. All authors have read and approved the final version of the manuscript. FL and JL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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