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Systematic Review

Oncological and Reproductive Outcomes in Premenopausal Women With Endometrial Hyperplasia with or without Atypia: A Meta-Analysis

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Abstract

Background: During follow-up, some patients with endometrial hyperplasia (EH) progress to endometrial cancer (EC) while others diagnosed with EH experience pathological escalation following hysterectomy. When treating premenopausal women, it is imperative to consider reproductive function, especially if they wish to preserve fertility. **Methods**: This study adhered to the Network Meta-Analysis extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline. We screened the PubMed, Web of Science, Cochrane Library, and Embase databases to identify relevant studies published from inception through July 31, 2023. The methodological quality of the studies was evaluated using the Cochrane Collaboration's tool for evaluating risk of bias. RevMan version 5.3 software, provided by the Cochrane Collaboration, was used for statistical meta-analysis. **Results**: A total of 45 studies were selected for final analysis, including 9 randomized controlled trials. We identified a pooled complete response (CR) rate of 0.82 [95% confidence interval (CI): 0.78–0.86] among premenopausal patients with EH undergoing fertility preservation therapy. In addition, we identified a pooled assisted reproductive technology (ART) utilization rate of 0.30 (95% CI: 0.10–0.49) among premenopausal patients with EH receiving fertility preservation therapy. The pooled pregnancy rate and pooled live birth rate were 0.30 (95% CI: 0.24–0.37) and 0.24 (95% CI: 0.17–0.30), respectively. Finally, we performed a subgroup analysis in to investigate the outcomes associated with atypical forms of EH. **Conclusions**: Our analysis confirmed that fertility preservation in premenopausal patients with EH is effective. Following treatment, some patients achieved satisfactory fertility outcomes, while others required ART support. Despite these findings, natural conception remained the primary mode of conception. **Registration**: The study has been registered on https://www.crd.york.ac.uk/prospero/ (registration number: CRD42023433030; registration link: https://www.crd.york.ac.uk/PROSPERO/view/CRD42023433030).

Keywords: endometrial hyperplasia; fertility preservation; reproductive outcomes; complete response

1. Introduction

Endometrial hyperplasia (EH) is a hyperplastic endometrial lesion, involving irregular gland size, increased glands, and an increased glandular interstitial ratio [1]. EH can be divided into two distinct categories: EH without atypia and atypical endometrial hyperplasia (AEH), also referred to as endometrial intraepithelial neoplasia (EIN), which is known to be associated with a 1%–43% risk of malignant progression [2]. This two-tier model of EH was endorsed by the World Health Organization (WHO) Classification of Female Reproductive Tumors in 2014 [3].

Endometrial cancer (EC) represents one of the most significant tumors of the reproductive system in women, and represents the sixth most common form of cancer in women, with 417,000 new cases reported globally in 2020 [4]. Over the past 30 years, the overall incidence of EC has increased by 132% [5]. Most ECs occur after menopause, but as many as 14% occur before menopause (4% before the age of 40 years) [6]. During follow-up, some cases of EH can progress further to EC while some patients diagnosed with EH experience pathological escalation after hysterectomy, concurrent with the detection of EC. The primary prevention of EH in high-risk populations, as well as the timely detection and standardized treatment of women who have already been diagnosed with EH, are essential if we are to improve the overall prognosis and reproductive outcomes of these young patients. For any disease, primary prevention should be regarded as the most important aspect, and relevant measures can obtain maximum benefit by protecting health status with relatively little loss, including financial costs and physical pain.

There are several risk factors for EH, including obesity (especially the presence of abdominal fat), exogenous estrogen supplementation (unsupported or under-supported by progesterone), and polycystic ovarian syndrome (PCOS) [7–12]. These risk factors apply to women of all ages, including both premenopausal and postmenopausal women. Women who have these risk factors but have not yet developed EH should regularly undergo endometrial screening. The primary prevention of EH is to control and standardize the treatment of the risk factors involved. Relevant measures include, but are not limited to, controlling the percentage of body fat (especially the consumption of abdominal fat and visceral fat) through exercise or by an appropriate diet, the careful use exogenous estrogens, and complete response outcome treatment of the intima with a sufficient amount and full cycle of progesterone if necessary [9,13–18]. In addition to these factors, attention should be paid to blood glucose (hyperinsulinemia) in patients who have been diagnosed with PCOS. The frequency of routine intima-related health examinations (mainly ultrasound) should also be increased [19].

Abnormal uterine bleeding (AUB) remains the primary clinical manifestation of EH, including infertility problems in women of reproductive age [20,21]. Premenopausal women do have a regular menstrual cycle [22]; therefore, ultrasound examination, using endometrial thickness as the main evaluation criteria, is not applicable [19,23]. There are currently no guidelines to recommend invasive testing in premenopausal women based on a single ultrasound report of a thickened endometrium [24,25]. Therefore, endometrial ultrasonography for premenopausal women should pay special attention to endometrial blood flow and endometrial proliferation. In the presence of clinical symptoms, especially ultrasound abnormalities, once EH (or even EC) is suspected, endometrial biopsy is recommended for a definitive diagnosis in order to provide more timely treatment measures. The treatment measures for EH should be comprehensively considered according to the age of the patient and the atypia of the cells in the pathological report; in other words, whether the patient has AEH or EIN. Especially for pre-menopausal women, and particularly those with no reproductive history, it is also necessary to consider whether they have the intention to continue to have children after EH treatment, and undertake a comprehensive assessment to determine whether fertility preservation treatment is required [1].

Providing timely evaluation and treatment for existing fertility preservation protocols without compromising cancer treatment has become an important aspect of modern oncology care [26]. The same applies to EH, a precursor of EC. When considering fertility preservation for EC, it is also necessary to consider the impact of chemotherapy and radiotherapy on ovarian function [27–30]; this is not a consideration for patients with EH.

Current treatments for reproductive preservation in EH remain limited, and predominantly include progesterone therapy, which involves oral progesterone and the intrauterine placement of a levonorgestrel intrauterine sustained release system (LNS-IUS), and hysteroscopic lesions [31].

The vast majority of studies relating to fertility preservation for endometrial lesions have focused on patients with AEH and highly differentiated early-stage endometrioid endometrial carcinoma (EEC). Previous literature reviews and meta-analyses of the effects of fertility preservation therapy in EH patients only focused on AEH and were considered coincident with high-level EEC [32–37].

Although the degree of cell differentiation in high-grade EEC is relatively high, this type of tumor is still malignant. No previous literature reviews or meta-analyses have focused on gynecological outcomes, such as endometrial complete response (CR) rate and obstetric outcomes (such as pregnancy and the live birth of offspring) in premenopausal women with precancerous EC lesions (i.e., EH) receiving fertility preservation therapy.

In the present study, we focused upon premenopausal patients with EH, including non-atypical EH and AEH. We reviewed previous studies on this type of patient receiving fertility preservation treatment and performed metanalysis on the effects of fertility preservation treatment on premenopausal patients with EH, especially those with strong fertility intention, including whether a satisfactory reproductive outcome was achieved.

2. Methods

This study followed the Meta-Analysis extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline [38].

2.1 Search Strategy

We screened the PubMed, Web of Science, Cochrane Library, and Embase databases to identify relevant studies that had been published from inception to the 31st of July 2023. Our literature searches featured a combination of subject-heading and keyword searches. Search terms included “fertility”, “endometrial hyperplasia”, “oral levonorgestrel”, “Levonorgestrel intrauterine sustained release system”, “LNS-IUS”, “metformin”, “medroxyprogesterone acetate” (MPA), “megestrol acetate” (MA), “progesterone”, “norethisterone” (NET), “dydrogesterone” and “reproductive”. The retrieved studies were limited to prospective studies, retrospective studies and randomized controlled trials (RCTs), with no language or site restrictions.

PubMed Search: ((FERTILITY) OR (reproductive)) AND (Endometrial hyperplasia); (“fertiles” OR “fertility”[MeSH Terms] OR “fertility” OR “fertile” OR “fertilities” OR (“reproduction”[MeSH Terms] OR “reproduction” OR “reproductions” OR “reproductive” OR “reproductively” OR “reproductives” OR “reproductivity”)) AND

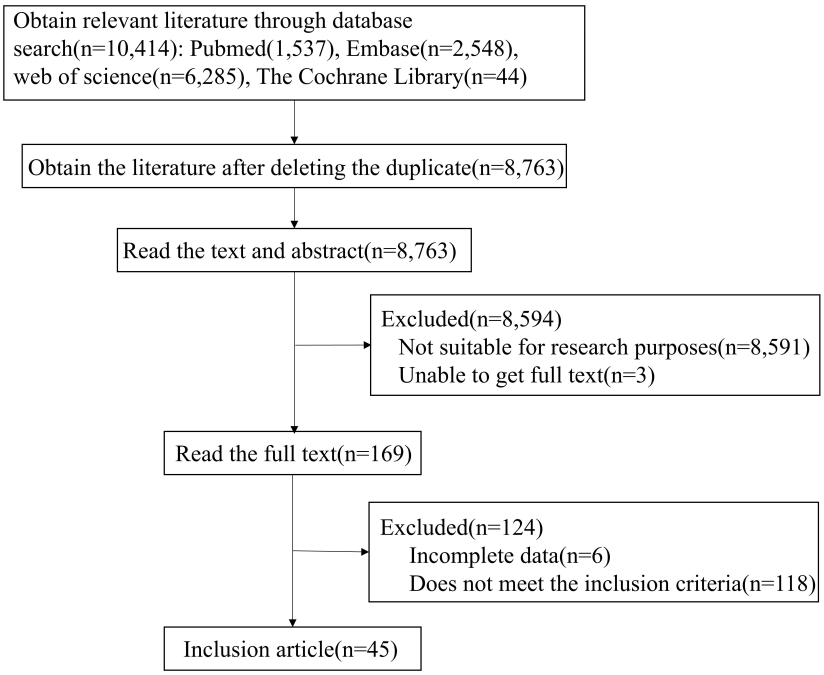


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

("endometrial hyperplasia"[MeSH Terms] OR ("endometrial" AND "hyperplasia") OR "endometrial hyperplasia"). Embase Search: ('fertility'/exp OR fertility OR reproductive) AND ('endometrial hyperplasia'/exp OR 'endometrial hyperplasia' OR (endometrial AND ('hyperplasia'/exp OR hyperplasia))). Cochrane Library Search: ((FERTILITY) OR (reproductive)) AND (Endometrial hyperplasia). Web of Science Search: AB = ((FERTILITY OR reproductive) AND Endometrial hyperplasia) OR TS = ((FERTILITY OR reproductive) AND Endometrial hyperplasia).

The diagnostic criteria for EH was in accordance with the WHO Classification of Female Reproductive Tumors [39]. In addition, the specific diagnostic criteria were adjusted according to the year in which the published study was conducted. Literature published in languages other than Chinese and English were translated by a professional translator.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria for meta-analysis were as follows: (1) the patients diagnosed with EH had been confirmed histologically; (2) the types of interventions included LNS-IUS or oral progesterone or other oral drugs (e.g., metformin); (3) the study included relevant outcomes for endometrial regression, and (4) premenopausal women.

The exclusion criteria were as follows: (1) the study design did not qualify as a controlled or observational study (thus excluding reviews, letters, and others); (2) the study did not meet the diagnostic criteria for EH (such as EC); (3) patients with comorbidities, such as severe kidney disease, or liver disease, and (4) postmenopausal patients.

2.3 Data Extraction and Quality Evaluation

Two evaluators independently searched the databases and identified relevant literature based on the inclusion and exclusion criteria. For each study retrieved, the evaluators recorded the name of the first author, the year of publication, the country in which the study was conducted, the methods used to preserve fertility function, treatment-time, follow-up time, the demographics of the subjects (sample size, age), and outcomes (primary and secondary results).

The methodological quality of the study was evaluated in accordance with the Cochrane Collaboration's tool for assessing the risk of bias [40]. This evaluation included random sequence generation, allocation concealment, subject and intervention provider blinding, outcome evaluation blinding, outcome data integrity, selective outcome reporting, and other sources of bias. Disagreement was judged by discussion. In accordance with the Cochrane Collaboration Group criteria, we divided the retrieved studies into three categories: (1) a low risk of bias (in all areas); (2) an unclear risk of bias (in one or more key areas), and (3) a high risk of bias (in one or more key areas).

2.4 Statistical Analysis

RevMan version 5.3 software (The Nordic Cochrane, Centre, Copenhagen) (https://revman.cochrane.org/), provided by the Cochrane Collaboration, was used for all statistical meta-analyses, and the relative risk (RR) difference and standard error (SE), along with the mean difference and 95% confidence interval (CI) were used as evaluation indices.

Table 1. Basic characteristics of the included studies.

No.	First author	Year	Study type	County	Age (years) (95% CI)	Treatment type	Treatment time (months)	Follow-up time (months)	EH type
1	Mitsuhashi A [40]	2019	retrospective	Japan	35.00 (26.00–44.00)	MPA plus metformin	6.00 (3.00–18.00)	57.00 (13.00–88.00)	AEH
2	Tabrizi AD [41]	2014	prospective	Iran	pre-menopausal	Metformin or MA	3.00	3.00	EH non-atypical
3	Simpson AN [42]	2014	prospective	Canada	36.50 (26.00–44.00)	oral progestin	9.50 (2.00–53.00)	39.00 (5.00–128.00)	AEH
4	Yang B [43]	2018	retrospective	China	33.00 (21.00–54.00)	oral MA or plus metformin	6.00 $\pm$ 0.30 (1.00–15.00)	unclear	AEH
5	Yang B [44]	2019	retrospective	China	32.00 (22.00–47.00)	MA, MA + metformin, LNG-IUD, Diane-35, MA + LNG-IUD	6.80 $\pm$ 0.40 (1.00–18.00)	13.50 (1.00–36.00)	AEH
6	Yang BY [45]	2020	RCT	China	18.00–45.00	MA or MA plus metformin	16.00	24.00	AEH
7	Ricciardi E [46]	2012	prospective	Italy	30.00 (25.00–40.00)	MA or MPA	12.00	4.00–24.00	AEH
8	Behnamfar F [47]	2014	RCT	Iran	38.40 $\pm$ 4.80	LNG-IUS or MPA	3.00	3.00	EH non-atypical
9	Sharifzadeh F [48]	2017	RCT	UK	pre-menopausal	MA or MA plus metformin	3.00	3.00	EH non-atypical
10	Brownfoot FC [49]	2014	retrospective	Australia	37.00 $\pm$ 7.60	MPA or LNG-IUS	12.00	24.00 (10.00–120.00)	AEH
11	Abu Hashim H [50]	2013	RCT	Egypt	pre-menopausal	LNG-IUS plus NET	3.00–6.00	3.00–12.00	EH non-atypical
12	Li H [51]	2008	prospective	China	32.60 (27.00–38.00)	letrozole	3.00	3.00	EH non-atypical
13	Zhou H [52]	2017	retrospective	China	average 30.60	GnRHa with LNG-IUD or GnRHa with letrozole	4.50 $\pm$ 1.90	18.70 (5.60–54.90)	AEH
14	Gallos ID [53]	2013	prospective	UK	Younger than 40.00	LNG-IUD or oral progestogens	6.00	58.80 (12.00–148.20)	EH non-atypical
15	Baek JS [54]	2016	retrospective	Korea	33.00 (20.00–41.00)	MA or MPA	3.00 (1.00–22.00)	8.00 (7.00–11.00)	AEH
16	Bian J [55]	2015	prospective	China	Younger than 40.00	LNG-IUS or non-LNG-IUS	6.00	6.00	EH non-atypical
17	Dolapcioglu K [56]	2013	RCT	Turkey	43.50 (40.00–55.00)	MPA or LNG-IUS	3.00	24.00	EH non-atypical
18	Kim MK [57]	2016	prospective	Korea	42.67 $\pm$ 8.35 (23.00–57.00)	LNG-IUS	9.00	12.00	EH non-atypical and AEH
19	Ushijima K [58]	2007	prospective	Japan	20.00–39.00	MPA with aspirin daily followed by cyclic estrogen-progestin therapy for 6 months or cyclic estrogen-progestin	6.00	3.00–6.00	AEH
20	Minig L [59]	2011	prospective	Spain	34.00 (22.00–40.00)	LNG-IUD + GnRH analogue	12.00	29.00 (4.00–102.00)	AEH
21	Karimi-Zarchi M [60]	2013	RCT	Iran	22.00–47.00	MPA or MPA with LNG-IUD	3.00	3.00	EH non-atypical
22	Signorelli M [61]	2009	prospective	Italy	32.00 (21.00–40.00)	danazole, GnRh analogue, natural progestin, MPA	4.00 (3.00–9.00)	98.00 (35.00–176.00)	AEH
23	El Behery MM [62]	2015	prospective	Egypt	30.00–50.00	Oral Progesterone or LNG-IUD	6.00	6.00	EH non-atypical
24	Koskas M [63]	2012	retrospective	France	28.00–40.00	Lynestrenol, megestrol acetate, medroxyprogesterone acetate, nomegestrol acetate, chlormadinone acetate	3.00–6.00	14.00–84.00	AEH
25	Yu M [64]	2009	retrospective	China	29.90	MPA, NET	7.30	34.60 (7.00–114.00)	AEH
26	Mentrikoski MJ [65]	2012	retrospective	USA	38.00 (25.00–39.00)	oral progestin or LNG-IUD	at least 6	7.00	AEH
27	Chen M [66]	2016	retrospective	China	32.00 (21.00–41.00)	MPA or MA	8.00 (2.00–18.00)	6.00 (3.00–24.00)	AEH

Table 1. Continued.

No.	First author	Year	Study type	County	Age (years) (95% CI)	Treatment type	Treatment time (months)	Follow-up time (months)	EH type
28	Mitsuhashi A [67]	2016	prospective	Japan	35.00 (26.00–41.00)	MPA or plus metformin	4.00–9.00	38.00 (9.00–66.00)	AEH
29	Ismail MT [68]	2013	RCT	Egypt	35.00–50.00	MPA or NET or LNG-IUS	3.00	3.00	EH non-atypical
30	Ohyagi-Hara C [33]	2015	retrospective	Japan	34.20 (22.20–43.90)	MPA	12.00	39.20 (3.40–153.80)	AEH
31	Ozdegirmenci O [69]	2011	RCT	Turkey	30.00–57.00	MPA, LYN and NET	3.00	6	EH non-atypical
32	Pashov AI [70]	2012	prospective	Russia	28.90 $\pm$ 4.30 (23.00–35.00)	LNG-IUS with GnRHa	3.00	48.37 $\pm$ 4.08 (24.00–72.00)	AEH
33	De Marzi P [71]	2015	retrospective	Italy	36.58 (23.00–43.00)	MA	3.00	25.00 (8.00–37.00)	AEH
34	Giampaolino P [72]	2019	retrospective	Italy	35.10 $\pm$ 4.80 (20.00–44.00)	LNG-IUS	1.00–6.00	1.00–6.00	AEH
35	Tamauchi S [73]	2018	retrospective	Japan	34.00 (19.00–45.00)	MPA	6.50 (2.50–15.80)	13.00 (4.00–32.00)	AEH
36	Lee SY [74]	2010	retrospective	Korea	39.10 (25.00–46.00)	LNG-IUS	4.50 (3.00–9.00)	3.00–30.00	EH non-atypical and AEH
37	Shan B [75]	2013	prospective	China	30.00 (18.00–38.00)	MA	6.00	17.00–54.00	AEH
38	Pronin SM [76]	2015	prospective	Russia	33.00 (28.00–42.00)	LNG-IUS	6.00	17.00 (1.00–45.00)	AEH
39	Acosta-Torres S [77]	2020	retrospective	USA	35.00 (30.00–38.50)	Progestin alone or with metformin	4.00 (3.40–7.40)	28.40 (17.20–61.60)	AEH
40	Randall TC [78]	1997	retrospective	USA	34.30 (25.00–39.00)	MA or MPA	9.00 (3.00–18.00)	40.10 (7.00–79.00)	AEH
41	Leone Roberti Maggiore U [79]	2019	retrospective	Italy	35.10 $\pm$ 5.30	LNG-IUS	6.70 $\pm$ 4.00	76.40 $\pm$ 48.80	AEH
42	Shan W [80]	2014	prospective	China	28.00–43.00	MA or MA plus metformin	12.00	12.00	AEH
43	Wheeler DT [81]	2007	retrospective	USA	34.00 (24.00–47.00)	oral progestin or progesterone, or LNG-IUS	3.00–6.00	11.00	AEH
44	Yang YF [82]	2015	retrospective	China	33.00 (24.00–39.00)	MA, MPA, LNG-IUS, NET	6.00 (3.00–13.00)	52.00 (8.00–78.00)	AEH
45	Zhou R [83]	2015	RCT	China	30.40 (20.00–40.00)	oral progestin	6.00 (1.00–41.50)	32.50 (10.00–92.00)	AEH

AEH, atypical endometrial hyperplasia; EH, endometrial hyperplasia; GnRHa, gonadotropin-releasing hormone analogue; LNG-IUS, levonorgestrel-releasing intrauterine system; LNG-IUD, levonorgestrel-releasing intrauterine device; MA, megestrol acetate; MPA, medroxyprogesterone acetate; LYN, lynestrenol; NET, norethisterone acetate; RCT, randomized controlled trial.

First, the Chi-squared test was used to assess heterogeneity; then the existence of heterogeneity (I^2) was quantitatively analyzed ($I^2 > 50\%$). Meta-analysis was performed without heterogeneity. When statistical heterogeneity existed among the study results, the source of heterogeneity was further analyzed, the influence of obvious clinical heterogeneity was excluded, and a random effects model was adopted. When there was no statistical heterogeneity among the results, a fixed effects model was applied. Finally, funnel maps were created by RevMan version 5.3 software to detect publication bias.

3. Results

3.1 Study Selection

We screened the PubMed, Web of Science, Cochrane Library, and Embase databases to identify relevant studies that had been published from inception to the 31st of July 2023. At the beginning of the study, we identified a total of 10,414 relevant articles based on the search strategy. After the two researchers independently read and screened the research data, a total of 44 studies [40–83] were selected for the final investigation. The literature screening process and results are shown in Fig. 1.

3.2 Basic Characteristics and Quality of the Selected Literature

The basic features of the included studies are shown in Table 1 (Ref. [33,40–83]) while the oncological and reproductive outcomes in pre-menopausal EH women with or without atypical EH are shown in Table 2 (Ref. [33,40–83]). The quality of the literature was evaluated using the Cochrane risk of bias tool [39]; analysis showed that the main sources of potential bias were the blinding of subjects and intervention providers (Fig. 2). The included studies were published between 1997 and 2023. Nine of the studies were high quality RCTs [45,47,48,50,56,60,68,69,83].

3.3 Complete Response (CR) in EH Women With or Without Atypical EH

Fig. 3 shows the pooled CR in premenopausal EH women with or without atypical EH who were treated with fertility-preservation therapy. There was a pooled CR rate of 0.82 (95% CI: 0.78–0.86) in premenopausal EH patients receiving fertility preservation therapy. Since endometrial cell atypia is related to treatment effect, we conducted subgroup analysis on whether EH has atypical. The pooled CR rate of EH patients without atypical EH was 0.83 (95% CI: 0.75–0.90); in comparison, the pooled CR rate for patients with AEH was 0.81 (95% CI: 0.76–0.87).

3.4 Reproductive Outcomes in EH Women With or Without Atypical EH

Fig. 4 shows the reproductive outcomes in premenopausal EH women with or without atypical EH who were treated with fertility-preservation treatment. There was a pooled assisted reproductive technology (ART) rate of 0.30 (95% CI: 0.10–0.49) in premenopausal EH patients receiving fertility preservation therapy. The pooled pregnancy rate and pooled live birth rate were 0.30 (95% CI: 0.24–0.37) and 0.24 (95% CI: 0.17–0.30), respectively.

Since only one article reported the obstetric outcomes of atypical EH, we only conducted subgroup analysis on the reproductive outcomes of patients with AEH. There was a pooled ART rate of 0.22 (95% CI: 0.15–0.29) in premenopausal patients with AEH receiving fertility preservation therapy. The pooled pregnancy rate and pooled live birth rate were 0.30 (95% CI: 0.23–0.37) and 0.23 (95% CI: 0.16–0.30), respectively.

3.5 Publication Bias

Fig. 5 shows an adjusted funnel diagram, including the endometrial CR rate, ART rate, pregnancy rate and live birth rate. All studies shown on the funnel maps were symmetrically distributed with respect to the vertical line, thus indicating that there were no significant small-sample effects or publication bias.

4. Discussion

A total of 45 previous studies (including prospective studies, retrospective studies, and high-quality RCTs) were included in this study. Two studies included non-atypical EH and AEH, 12 studies focused on non-atypical EH only, and 31 studies focused on EH and AEH only. The study participants ranged from 18 to 57 years-of-age, and fertility preservation treatments included oral progesterone preparations (such as MPA/MA/NET) or the placement of an intrauterine LNG-IUS. The treatment period ranged from 1 to 53 months, and the follow-up period ranged from 1 to 176 months. The overall intimal pooled CR rate of premenopausal EH patients was 0.82 (95% CI: 0.78–0.86). The pooled CR rate of EH patients without atypical EH and AEH were 0.83 (95% CI: 0.75–0.80) and 0.81 (95% CI: 0.76–0.87), respectively. For reproductive outcomes (including ART, pregnancy, and live births), the overall pooled rates were 0.30 (95% CI: 0.10–0.49), 0.30 (95% CI: 0.24–0.37), and 0.24 (95% CI: 0.17–0.30), respectively. Since only one study reported the fertility outcome of atypical EH, we did not analyze the fertility outcome of this type of EH patients after undergoing fertility preservation therapy. For premenopausal AEH patients treated with fertility preservation, the fertility outcomes (including the pooled ART rate, the pooled pregnancy rate, and the pooled live birth rate) were 0.22 (95% CI: 0.15–0.29), 0.30 (95% CI: 0.23–0.37), and 0.23 (95% CI: 0.16–0.30), respectively.

Many drugs were described by the papers included in the present analysis. Different progesterone analogues exert differing metabolic pathways in the human body, which may provide patients with different degrees of side effects. The chemical name for MPA is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. The bioavailabil-

Table 2. Oncological and reproductive outcomes of women with endometrial hyperplasia with or without atypical.

No.	First author	EH non-atypical	CR	ART	Pregnancy	Live birth	AEH	CR	ART	Pregnancy	Live birth
1	Mitsuhashi A [40]	-	-	-	-	-	21	21	-	-	-
2	Tabrizi AD [41]	43	34	-	-	-	-	-	-	-	-
3	Simpson AN [42]	-	-	-	-	-	19	18	-	-	-
4	Yang B [43]	-	-	-	-	-	148	141	22	25	-
5	Yang B [44]	-	-	-	-	-	120	112	-	21	-
6	Yang BY [45]	-	-	-	-	-	123	79	-	-	-
7	Ricciardi E [46]	-	-	-	-	-	14	11	9	4	-
8	Behnamfar F [47]	55	44	-	-	-	-	-	-	-	-
9	Sharifzadeh F [48]	42	30	-	-	-	-	-	-	-	-
10	Brownfoot FC [49]	-	-	-	-	-	42	32	2	4	4
11	Abu Hashim H [50]	120	86	-	-	-	-	-	-	-	-
12	Li H [51]	5	5	-	-	-	-	-	-	-	-
13	Zhou H [52]	-	-	-	-	-	12	12		0	0
14	Gallos ID [53]	34	30	-	-	-	-	-	-	-	-
15	Baek JS [54]	-	-	-	-	-	18	16	4	3	2
16	Bian J [55]	190	117	171	64	53	-	-	-	-	-
17	Dolapcioglu K [56]	102	76	-	-	-	-	-	-	-	-
18	Kim MK [57]	32	30	-	-	-	6	6	-	-	-
19	Ushijima K [58]	-	-	-	-	-	17	14	-	-	-
20	Minig L [59]	-	-	-	-	-	20	19	2	11	0
21	Karimi-Zarchi M [60]	40	33	-	-	-	-	-	-	-	-
22	Signorelli M [61]	-	-	-	-	-	10	1	0	8	7
23	El Behery MM [62]	100	88	-	-	-	-	-	-	-	-
24	Koskas M [63]	-	-	-	-	-	14	13	5	6	5
25	Yu M [64]	-	-	-	-	-	17	14	13	7	3
26	Mentrikoski MJ [65]	-	-	-	-	-	7	5	-	-	-
27	Chen M [66]	-	-	-	-	-	16	12	9	9	6
28	Mitsuhashi A [67]	-	-	-	-	-	17	16	11	11	6
29	Ismail MT [68]	90	88	-	-	-	-	-	-	-	-
30	Ohyagi-Hara C [33]	-	-	-	-	-	11	9	2	5	7
31	Ozdegirmenci O [69]	82	80	-	-	-	-	-	-	-	-
32	Pashov AI [70]	-	-	-	-	-	13	13	0	0	0
33	De Marzi P [71]	-	-	-	-	-	20	13	1	6	5
34	Giampaolino P [72]	-	-	-	-	-	55	51	0	10	10
35	Tamauchi S [73]	-	-	-	-	-	30	26	8	11	7
36	Lee SY [74]	11	11	-	-	-	1	1	-	-	-
37	Shan B [75]	-	-	-	-	-	12	9	0	0	0
38	Pronin SM [76]	-	-	-	-	-	38	32	0	5	4
39	Acosta-Torres S [77]	-	-	-	-	-	54	41	7	9	9
40	Randall TC [78]	-	-	-	-	-	17	16	2	-	-
41	Leone Roberti Maggiore U [79]	-	-	-	-	-	28	25	2	6	5
42	Shan W [80]	-	-	-	-	-	16	8	-	-	-
43	Wheeler DT [81]	-	-	-	-	-	18	12	-	-	-
44	Yang YF [82]	-	-	-	-	-	37	34	-	-	-
45	Zhou R [83]	-	-	-	-	-	13	9	4	4	-

ART, assisted reproductive technology; CR, complete response; EH, endometrial hyperplasia.

ity of MPA is close to 100%. The common adverse events of MPA are the development of peripheral edema and an increased incidence of thromboembolic complications, primarily deep vein thrombosis of the lower extremities, although the latter occurs at relatively high doses of progesterone and is usually not severe. However, patients taking MPA are less likely to discontinue their medication due to adverse events [84]. The levonorgestrel-releasing intrauterine device (LNG-IUD) was first introduced in Finland in 1990 [85]. Recently updated guidelines recommend the

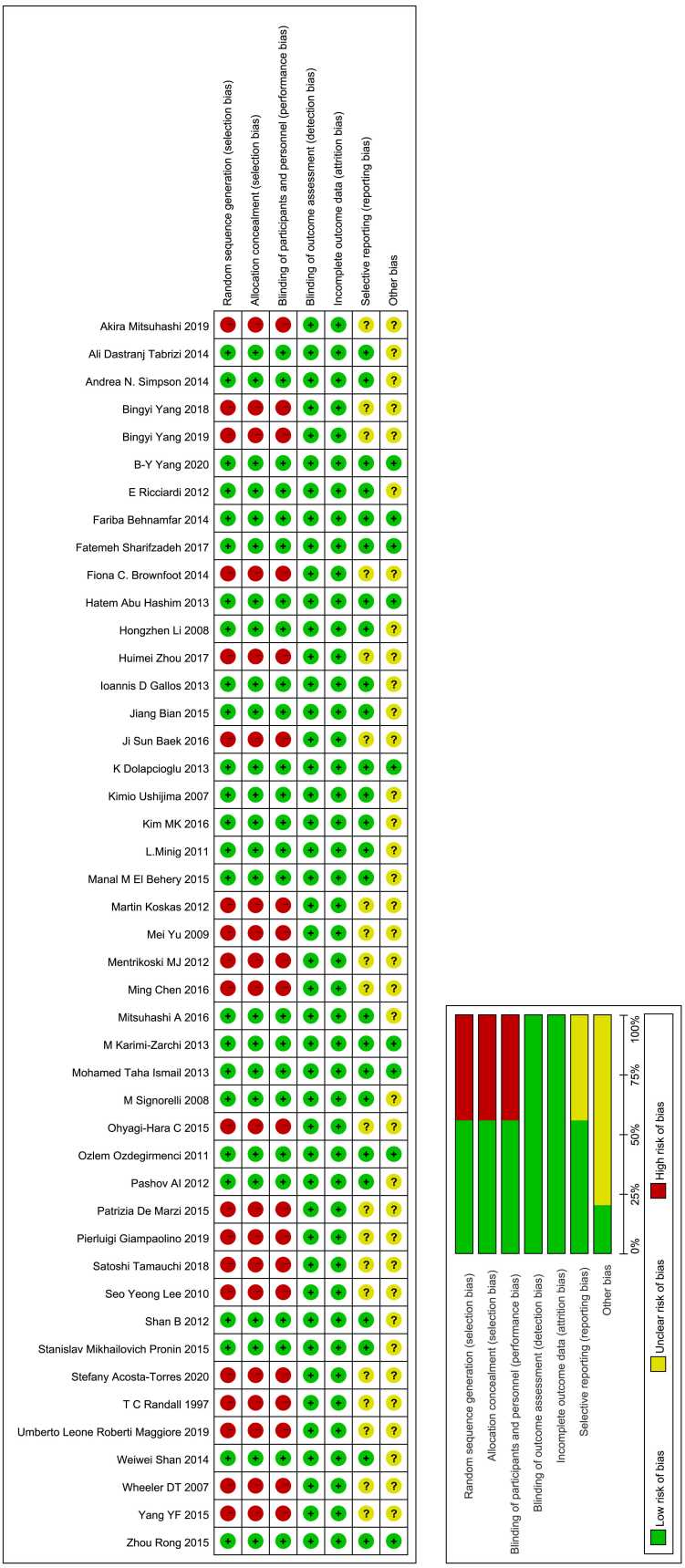


Fig. 2. Risk of bias and the clinical applicability of the included studies.

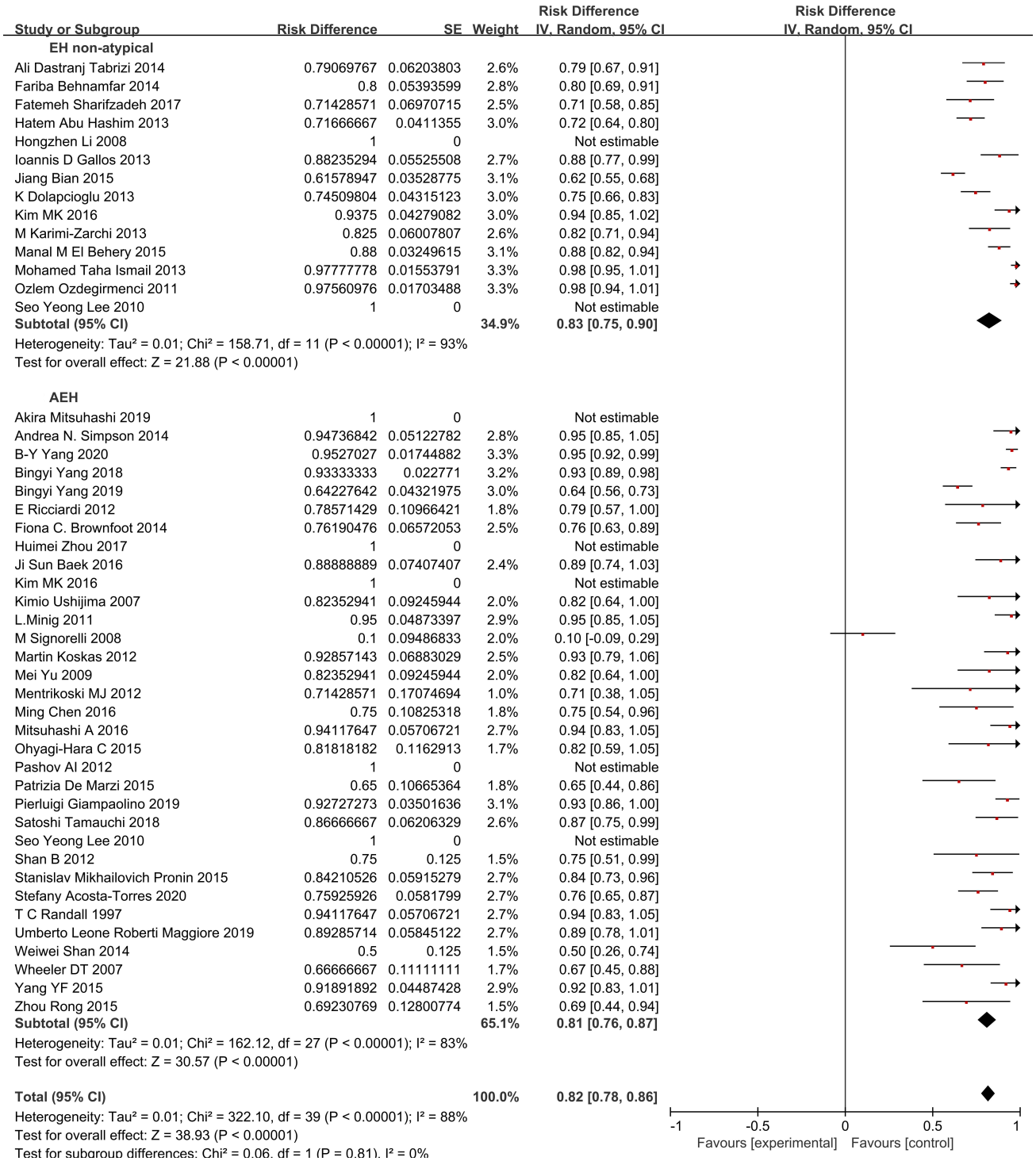
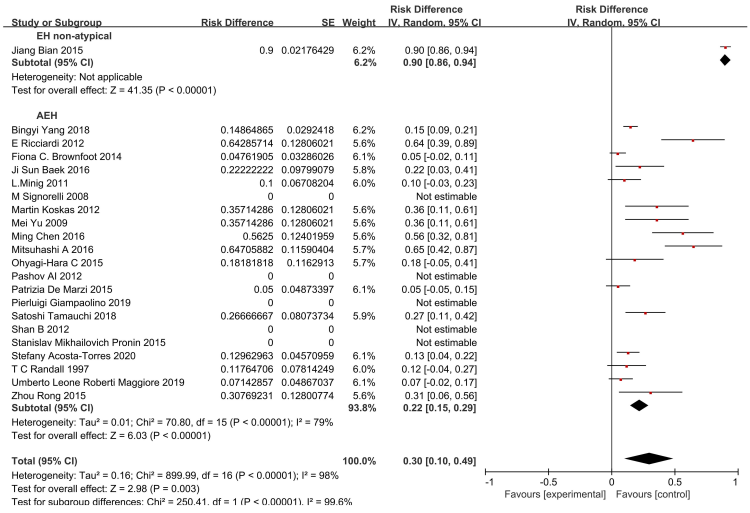


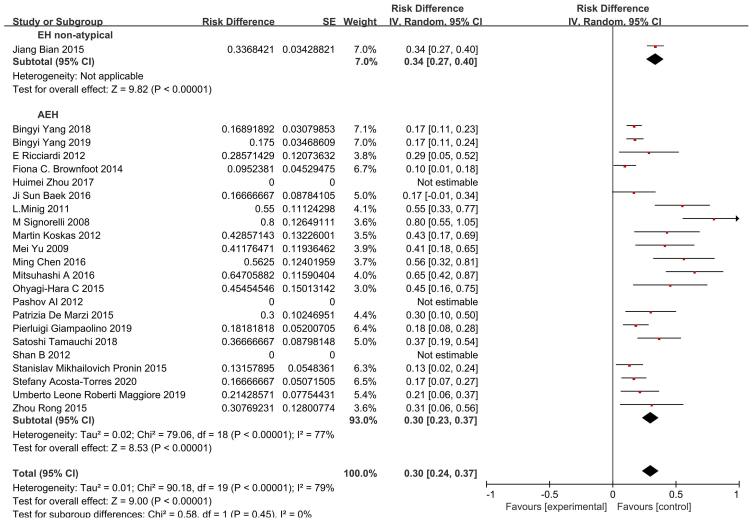
Fig. 3. Meta-analysis of complete response (CR) in women with endometrial hyperplasia with or without atypical hyperplasia (including subgroup analysis). EH, endometrial hyperplasia; AEH, atypical endometrial hyperplasia.

LNG-IUS as a first-line treatment for the absence of dysplastic endometrial hyperplasia [86,87]. Recent guidelines support the safety of the LNG-IUD system in adolescents, non-pregnant women, and perimenopausal women [88,89]. NET is partially converted (approximately 0.40% to 1.00%) to ethinylestradiol in the liver and therefore also generates estrogen effects in the body [90,91]. This conversion may be important with respect to the adverse effects that could be generated by NET [92]. The specific treatment plan for EH patients who wish to have children needs to be personalized and followed up closely.

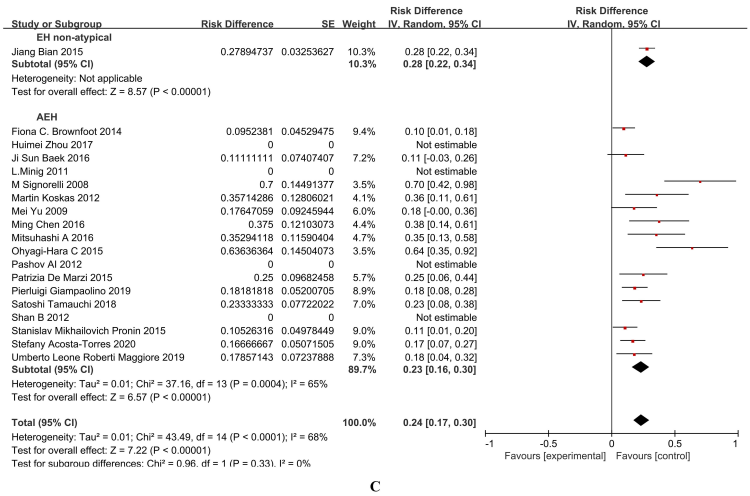
Previous literature reviews on the use of fertility preservation therapy in women with EH focused only on patients with AEH, including those with early-stage EEC



A



B



C

Fig. 4. Meta-analysis of reproductive outcomes for women with endometrial hyperplasia with or without atypical hyperplasia (including subgroup analysis). (A) Assisted reproductive technology (ART). (B) Pregnancy. (C) Live birth.

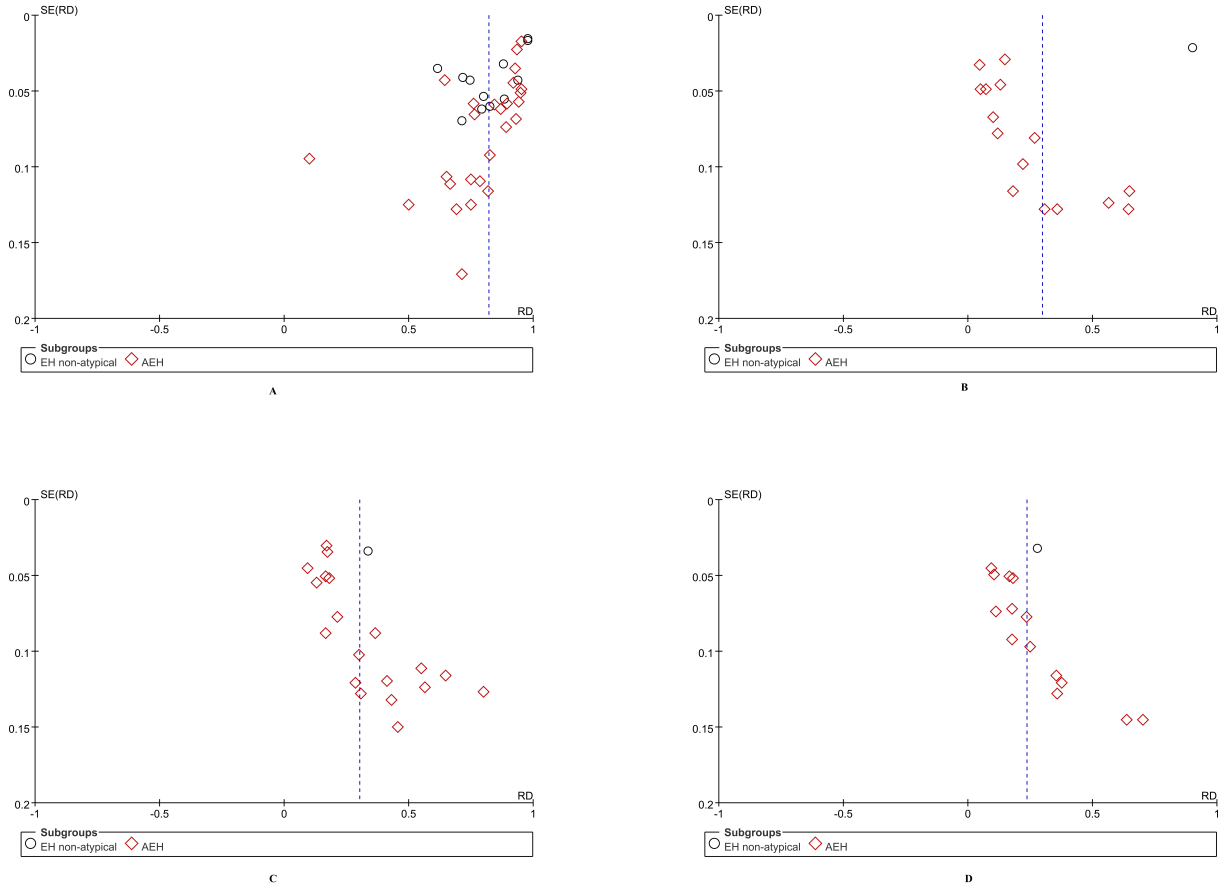


Fig. 5. Funnel plot. (A) Complete response (CR). (B) Assisted reproductive technology (ART). (C) Pregnancy. (D) Live birth. RD, relative distance.

[32,34–36]. Although this specific cohort cannot represent the entire EH population, it can still partially indicate that fertility preservation therapy is effective for EH patients who wish to retain their fertility. The present study subclassified patients according to endometrial atypia; our AEH analysis generated data that were similar to those reported by previous studies. With regards to premenopausal women with non-atypical EH, it was evident that fertility preservation was effective with regards to the intima, and the comprehensive CR rate was close to that of patients with AEH. However, only one article has been published relating to the reproductive outcome of non-atypical EH [68]. This particular publication reported that the fertility outcomes (including ART, pregnancy and live birth) of EH patients without atypical after fertility preservation treatment were 0.90, 0.34, and 0.28, respectively; these rates were slightly higher than those of patients with AEH following fertility preservation treatment. However, further research is required to identify any statistical differences between these two types of patients.

In addition to utilizing the pregnancy rate and live birth rate as the main evaluation indicators, the health status of the offspring is also an issue that must be considered in terms of eugenic care. None of the studies with reported reproductive outcomes included in this meta-analysis reported health problems associated with their offspring. No previous study investigated whether the presence of maternal EH can exert an impact on the growth, development and long-term health of the offspring. However, it should be noted that some of the high-risk factors associated with EH disease will affect the growth and development of offspring and their long-term health, especially with regards to PCOS, hyperinsulinemia, diabetes, and obesity [93–96].

There are some limitations to this study that need to be considered. For example, this study only conducted meta-analysis on the gynecological outcome (CR rate) and obstetric outcomes (ART rate, pregnancy rate, live birth rate) of patients with EH following fertility preservation treatment, and did not conduct subgroup analysis on other factors associated with infertility, such as ovulation abnormalities or tubal factor infertility. In addition, we did not perform a comparative evaluation of different treatment modalities, such as drug types, medication modalities, or specific treatment regiments, and did not compare different pregnancy assistance regimens that may have been received by patients receiving ART. Therefore, our findings cannot pro-

vide recommendations for the treatment of patients with EH, including the treatment of EH and ART treatment. Furthermore, due to the content and quality limitations of the published literature, the results of the present study should be adopted cautiously. It is still necessary to investigate the fertility outcomes of the heterotypic EH population after receiving fertility preservation therapy. Finally, we must consider the final fertility outcomes of patients with EH as such outcomes will inevitably be associated with a range of influencing factors. Further research should include multicenter RCTs with strict designs and long follow-up periods in order to determine the best treatment plan.

5. Conclusions

According to the present meta-analysis, the use of fertility preservation treatment for premenopausal patients with EH was effective. Approximately, four-fifths of patients achieved complete endometrial regression after a certain cycle of treatment. After treatment, some of the patients achieved satisfactory fertility outcomes, some of which needed to be supported by ART technology, although natural conception was still the main method of conception. Fertility preservation treatment for women with EH who still wish to have children still needs to be confirmed. However, based on the studies included in our meta-analysis, we are unable to identify an optimal treatment plan. Furthermore, additional research is required to determine whether there was any difference in efficacy, including endometrial outcomes and satisfactory fertility outcomes, when compared between patients with AEH and non-atypical EH. Appropriate studies are still needed, especially those related to the fertility outcomes of patients with non-atypical EH.

Abbreviations

AEH, atypical endometrial hyperplasia; ART, assisted reproductive technology; AUB, abnormal uterine bleeding; CI, confidence interval; CR, complete response; EC, Endometrial cancer; EEC, endometrioid endometrial carcinoma; EH, endometrial hyperplasia; EIN, endometrial intraepithelial neoplasia; I^2, heterogeneity; LNS-IUS, levonorgestrel intrauterine sustained release system; LNG-IUD, levonorgestrel-releasing intrauterine device; MA, megestrol acetate; MPA, medroxyprogesterone acetate; LYN, lynestrenol; NET, norethisterone; PCOS, polycystic ovarian syndrome; PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized controlled trials; SE, standard error; RD, relative distance; WHO, world health organization.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

Author Contributions

JW, YY and RJ designed the research study. JW and YY performed the research. JW and YY analyzed the data, TW made substantial contributions to the interpretation of the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG39051.

References

[1] Ring KL, Mills AM, Modesitt SC. Endometrial Hyperplasia. Obstetrics and Gynecology. 2022; 140: 1061–1075. https://doi.org/10.1097/AOG.0000000000004989.

[2] Nees LK, Heublein S, Steinmacher S, Juhasz-Böss I, Brucker S, Tempfer CB, *et al*. Endometrial hyperplasia as a risk factor of endometrial cancer. Archives of Gynecology and Obstetrics. 2022; 306: 407–421. https://doi.org/10.1007/s00404-021-06380-5.

[3] Lu Z, Chen J. Introduction of WHO classification of tumours of female reproductive organs, fourth edition. Zhonghua Bing Li Xue Za Zhi = Chinese Journal of Pathology. 2014; 43: 649–650. (In Chinese)

[4] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a Cancer Journal for Clinicians. 2021; 71: 209–249. https://doi.org/10.3322/caac.21660.

[5] Gu B, Shang X, Yan M, Li X, Wang W, Wang Q, *et al*. Variations in incidence and mortality rates of endometrial cancer at the global, regional, and national levels, 1990-2019. Gynecologic Oncology. 2021; 161: 573–580. https://doi.org/10.1016/j.ygyno.2021.01.036.

[6] Ash SJ, Farrell SA, Flowerdew G. Endometrial biopsy in DUB. The Journal of Reproductive Medicine. 1996; 41: 892–896.

[7] Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. Lancet (London, England). 2014; 384: 755–765. https://doi.org/10.1016/S0140-6736(14)60892-8.

[8] Epplein M, Reed SD, Voigt LF, Newton KM, Holt VL, Weiss NS. Risk of complex and atypical endometrial hyperplasia in relation to anthropometric measures and reproductive history.

American Journal of Epidemiology. 2008; 168: 563–570; discussion 571–576. https://doi.org/10.1093/aje/kwn168.

[9] Modesitt SC, Hallowell PT, Slack-Davis JK, Michalek RD, Atkins KA, Kelley SL, *et al*. Women at extreme risk for obesity-related carcinogenesis: Baseline endometrial pathology and impact of bariatric surgery on weight, metabolic profiles and quality of life. Gynecologic Oncology. 2015; 138: 238–245. https://doi.org/10.1016/j.ygyno.2015.05.015.

[10] Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Human Reproduction Update. 2014; 20: 748–758. https://doi.org/10.1093/humupd/dmu012.

[11] Shan W, Ning C, Luo X, Zhou Q, Gu C, Zhang Z, *et al*. Hyperinsulinemia is associated with endometrial hyperplasia and disordered proliferative endometrium: a prospective cross-sectional study. Gynecologic Oncology. 2014; 132: 606–610. https://doi.org/10.1016/j.ygyno.2014.01.004.

[12] Wise MR, Gill P, Lensen S, Thompson JMD, Farquhar CM. Body mass index trumps age in decision for endometrial biopsy: cohort study of symptomatic premenopausal women. American Journal of Obstetrics and Gynecology. 2016; 215: 598.e1–598.e8. https://doi.org/10.1016/j.ajog.2016.06.006.

[13] Anveden Å, Taube M, Peltonen M, Jacobson P, Andersson-Assarsson JC, Sjöholm K, *et al*. Long-term incidence of female-specific cancer after bariatric surgery or usual care in the Swedish Obese Subjects Study. Gynecologic Oncology. 2017; 145: 224–229. https://doi.org/10.1016/j.ygyno.2017.02.036.

[14] Campagnoli C, Abbà C, Ambroggio S, Brucato T, Pasanisi P. Life-style and metformin for the prevention of endometrial pathology in postmenopausal women. Gynecological Endocrinology: the Official Journal of the International Society of Gynecological Endocrinology. 2013; 29: 119–124. https://doi.org/10.3109/09513590.2012.706671.

[15] Linkov F, Edwards R, Balk J, Yurkovetsky Z, Stadterman B, Lokshin A, *et al*. Endometrial hyperplasia, endometrial cancer and prevention: gaps in existing research of modifiable risk factors. European Journal of Cancer (Oxford, England: 1990). 2008; 44: 1632–1644. https://doi.org/10.1016/j.ejca.2008.05.001.

[16] Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. Molecular Oncology. 2021; 15: 790–800. https://doi.org/10.1002/1878-0261.12772.

[17] Derbyshire AE, Allen JL, Gittins M, Lakhiani B, Bolton J, Shaw J, *et al*. PROgesterone Therapy for Endometrial Cancer Prevention in Obese Women (PROTEC) Trial: A Feasibility Study. Cancer Prevention Research (Philadelphia, Pa.). 2021; 14: 263–274. https://doi.org/10.1158/1940-6207.CAPR-20-0248.

[18] Lu KH, Loose DS, Yates MS, Nogueras-Gonzalez GM, Munsell MF, Chen LM, *et al*. Prospective multicenter randomized intermediate biomarker study of oral contraceptive versus depoprovera for prevention of endometrial cancer in women with Lynch syndrome. Cancer Prevention Research (Philadelphia, Pa.). 2013; 6: 774–781. https://doi.org/10.1158/1940-6207.CAPR-13-0020.

[19] Gerritzen LHM, Hoogerbrugge N, Oei ALM, Nagengast FM, van Ham MAPC, Massuger LFAG, *et al*. Improvement of endometrial biopsy over transvaginal ultrasound alone for endometrial surveillance in women with Lynch syndrome. Familial Cancer. 2009; 8: 391–397. https://doi.org/10.1007/s10689-009-9252-x.

[20] Marnach ML, Laughlin-Tommaso SK. Evaluation and Management of Abnormal Uterine Bleeding. Mayo Clinic Proceedings. 2019; 94: 326–335. https://doi.org/10.1016/j.mayocp.2018.12.012.

[21] Whitaker L, Critchley HOD. Abnormal uterine bleeding. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2016; 34: 54–65. https://doi.org/10.1016/j.bpobgyn.2015.11.012.

[22] Alcázar JL, Bonilla L, Marucco J, Padilla AI, Chacón E, Manzour N, *et al*. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness $\geq$11 mm: A systematic review and meta-analysis. Journal of Clinical Ultrasound: JCU. 2018; 46: 565–570. https://doi.org/10.1002/jcu.22631.

[23] Leitao MM, Jr, Han G, Lee LX, Abu-Rustum NR, Brown CL, Chi DS, *et al*. Complex atypical hyperplasia of the uterus: characteristics and prediction of underlying carcinoma risk. American Journal of Obstetrics and Gynecology. 2010; 203: 349.e1–6. https://doi.org/10.1016/j.ajog.2010.05.004.

[24] Ghoubara A, Emovon E, Sundar S, Ewies A. Thickened endometrium in asymptomatic postmenopausal women - determining an optimum threshold for prediction of atypical hyperplasia and cancer. Journal of Obstetrics and Gynaecology: THe Journal of the Institute of Obstetrics and Gynaecology. 2018; 38: 1146–1149. https://doi.org/10.1080/01443615.2018.1458081.

[25] Bedner R, Rzepka-Górska I. Hysteroscopy with directed biopsy versus dilatation and curettage for the diagnosis of endometrial hyperplasia and cancer in perimenopausal women. European Journal of Gynaecological Oncology. 2007; 28: 400–402.

[26] Taylan E, Oktay K. Fertility preservation in gynecologic cancers. Gynecologic Oncology. 2019; 155: 522–529. https://doi.org/10.1016/j.ygyno.2019.09.012.

[27] Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. Future Oncology (London, England). 2016; 12: 2333–2344. https://doi.org/10.2217/fon-2016-0176.

[28] Soleimani R, Heytens E, Darzynkiewicz Z, Oktay K. Mechanisms of chemotherapy-induced human ovarian aging: double strand DNA breaks and microvascular compromise. Aging. 2011; 3: 782–793. https://doi.org/10.18632/aging.100363.

[29] Wallace WHB, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. International Journal of Radiation Oncology, Biology, Physics. 2005; 62: 738–744. https://doi.org/10.1016/j.ijrobp.2004.11.038.

[30] Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. International Journal of Radiation Oncology, Biology, Physics. 2009; 73: 1304–1312. https://doi.org/10.1016/j.ijrobp.2008.12.016.

[31] Abu-Rustum NR, Yashar CM, Bradley K, Campos SM, Chino J, Chon HS, *et al*. NCCN Guidelines® Insights: Uterine Neoplasms, Version 3.2021. Journal of the National Comprehensive Cancer Network: JNCCN. 2021; 19: 888–895. https://doi.org/10.6004/jnccn.2021.0038.

[32] Wei J, Zhang W, Feng L, Gao W. Comparison of fertility-sparing treatments in patients with early endometrial cancer and atypical complex hyperplasia: A meta-analysis and systematic review. Medicine. 2017; 96: e8034. https://doi.org/10.1097/MD.0000000000008034.

[33] Ohyagi-Hara C, Sawada K, Aki I, Mabuchi S, Kobayashi E, Ueda Y, *et al*. Efficacies and pregnant outcomes of fertility-sparing treatment with medroxyprogesterone acetate for endometrioid adenocarcinoma and complex atypical hyperplasia: our experience and a review of the literature. Archives of Gynecology and Obstetrics. 2015; 291: 151–157. https://doi.org/10.1007/s00404-014-3417-z.

[34] Chae-Kim J, Garg G, Gavrilova-Jordan L, Blake LE, Kim TT, Wu Q, *et al*. Outcomes of women treated with progestin and metformin for atypical endometrial hyperplasia and early endometrial cancer: a systematic review and meta-analysis. In-

ternational Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 2021; 31: 1499–1505. https://doi.org/10.1136/ijgc-2021-002699.

[35] Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. American Journal of Obstetrics and Gynecology. 2012; 207: 266.e1–12. https://doi.org/10.1016/j.ajog.2012.08.011.

[36] De Rocco S, Buca D, Oronzii L, Petrillo M, Fanfani F, Nappi L, *et al*. Reproductive and pregnancy outcomes of fertility-sparing treatments for early-stage endometrial cancer or atypical hyperplasia: A systematic review and meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2022; 273: 90–97. https://doi.org/10.1016/j.ejogrb.2022.04.019.

[37] Bilir E, Kahramanoğlu İ. The role of hysteroscopy in fertility preservation in endometrial cancer and atypical endometrial hyperplasia: a semi-systematic literature review. Archives of Gynecology and Obstetrics. 2023; 308: 1113–1126. https://doi.org/10.1007/s00404-023-06960-7.

[38] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical Research Ed.). 2021; 372: n71. https://doi.org/10.1136/bmj.n71.

[39] Savović J, Weeks L, Sterne JAC, Turner L, Altman DG, Moher D, *et al*. Evaluation of the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation. Systematic Reviews. 2014; 3: 37. https://doi.org/10.1186/2046-4053-3-37.

[40] Mitsuhashi A, Habu Y, Kobayashi T, Kawarai Y, Ishikawa H, Usui H, *et al*. Long-term outcomes of progestin plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer patients. Journal of Gynecologic Oncology. 2019; 30: e90. https://doi.org/10.3802/jgo.2019.30.e90.

[41] Tabrizi AD, Melli MS, Foroughi M, Ghojazadeh M, Bidadi S. Antiproliferative effect of metformin on the endometrium–a clinical trial. Asian Pacific Journal of Cancer Prevention: APJCP. 2014; 15: 10067–10070. https://doi.org/10.7314/apjcp.2014.15.23.10067.

[42] Simpson AN, Feigenberg T, Clarke BA, Gien LT, Ismiil N, Laframboise S, *et al*. Fertility sparing treatment of complex atypical hyperplasia and low grade endometrial cancer using oral progestin. Gynecologic Oncology. 2014; 133: 229–233. https://doi.org/10.1016/j.ygyno.2014.02.020.

[43] Yang B, Xie L, Zhang H, Zhu Q, Du Y, Luo X, *et al*. Insulin resistance and overweight prolonged fertility-sparing treatment duration in endometrial atypical hyperplasia patients. Journal of Gynecologic Oncology. 2018; 29: e35. https://doi.org/10.3802/jgo.2018.29.e35.

[44] Yang B, Xu Y, Zhu Q, Xie L, Shan W, Ning C, *et al*. Treatment efficiency of comprehensive hysteroscopic evaluation and lesion resection combined with progestin therapy in young women with endometrial atypical hyperplasia and endometrial cancer. Gynecologic Oncology. 2019; 153: 55–62. https://doi.org/10.1016/j.ygyno.2019.01.014.

[45] Yang BY, Gulinazi Y, Du Y, Ning CC, Cheng YL, Shan WW, *et al*. Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial. BJOG: an International Journal of Obstetrics and Gynaecology. 2020; 127: 848–857. https://doi.org/10.1111/1471-0528.16108.

[46] Ricciardi E, Maniglio P, Frega A, Marci R, Caserta D, Moscarini M. Fertility-sparing treatment of endometrial cancer precursors among young women: a reproductive point of view. European Review for Medical and Pharmacological Sciences. 2012; 16: 1934–1937.

[47] Behnamfar F, Ghahiri A, Tavakoli M. Levonorgestrel-releasing intrauterine system (Mirena) in compare to medroxyprogesterone acetate as a therapy for endometrial hyperplasia. Journal of Research in Medical Sciences: the Official Journal of Isfahan University of Medical Sciences. 2014; 19: 686–690.

[48] Sharifzadeh F, Aminimoghaddam S, Kashanian M, Fazaeli M, Sheikhansari N. A comparison between the effects of metformin and megestrol on simple endometrial hyperplasia. Gynecological Endocrinology: the Official Journal of the International Society of Gynecological Endocrinology. 2017; 33: 152–155. https://doi.org/10.1080/09513590.2016.1223285.

[49] Brownfoot FC, Hickey M, Ang WC, Arora V, McNally O. Complex atypical hyperplasia of the endometrium: differences in outcome following conservative management of pre-and postmenopausal women. Reproductive Sciences. 2014; 21: 1244–1248. https://doi.org/10.1177/1933719114522517.

[50] Abu Hashim H, Zayed A, Ghayaty E, El Rakhawy M. LNG-IUS treatment of non-atypical endometrial hyperplasia in perimenopausal women: a randomized controlled trial. Journal of Gynecologic Oncology. 2013; 24: 128–134. https://doi.org/10.3802/jgo.2013.24.2.128.

[51] Li H, Chen X, Qiao J. Letrozole as primary therapy for endometrial hyperplasia in young women. International Journal of Gynecology & Obstetrics. 2008; 100: 10–12. https://doi.org/10.1016/j.ijgo.2007.06.0410.

[52] Zhou H, Cao D, Yang J, Shen K, Lang J. Gonadotropin-Releasing Hormone Agonist Combined With a Levonorgestrel-Releasing Intrauterine System or Letrozole for Fertility-Preserving Treatment of Endometrial Carcinoma and Complex Atypical Hyperplasia in Young Women. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 2017; 27: 1178–1182. https://doi.org/10.1097/IGC.0000000000001008.

[53] Gallos ID, Ganesan R, Gupta JK. Prediction of Regression and Relapse of Endometrial Hyperplasia with Conservative Therapy. Obstetrics & Gynecology. 2013; 121: 1165–1171. https://doi.org/10.1097/AOG.0b013e31828cb563.

[54] Baek JS, Lee WH, Kang WD, Kim SM. Fertility-preserving treatment in complex atypical hyperplasia and early endometrial cancer in young women with oral progestin: Is it effective? Obstetrics & Gynecology Science. 2016; 59: 24–31. https://doi.org/10.5468/ogs.2016.59.1.24.

[55] Bian J, Shao H, Liu H, Li H, Fang L, Xing C, *et al*. Efficacy of the Levonorgestrel-Releasing Intrauterine System on IVF-ET Outcomes in PCOS With Simple Endometrial Hyperplasia. Reproductive Sciences (Thousand Oaks, Calif.). 2015; 22: 758–766. https://doi.org/10.1177/1933719114561553.

[56] Dolapcioglu K, Boz A, Baloglu A. The efficacy of intrauterine versus oral progestin for the treatment of endometrial hyperplasia. A prospective randomized comparative study. Clinical and Experimental Obstetrics & Gynecology. 2013; 40: 122–126.

[57] Kim MK, Seong SJ, Kim JW, Jeon S, Choi HS, Lee IH, *et al*. Management of Endometrial Hyperplasia With a Levonorgestrel-Releasing Intrauterine System: A Korean Gynecologic-Oncology Group Study. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 2016; 26: 711–715. https://doi.org/10.1097/IGC.0000000000000669.

[58] Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, *et al*. Multicenter phase ii study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. Journal of Clinical Oncology. 2007; 25: 2798–2803. https://doi.org/10.1200/JCO.

2006.08.8344.
[59] Minig L, Franchi D, Boveri S, Casadio C, Bocciolone L, Sideri M. Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. Annals of Oncology. 2011; 22: 643–649. https://doi.org10.1093/annonc/mdq463.
[60] Karimi-Zarchi M, Dehghani-Firoozabadi R, Tabatabaie A, Dehghani-Firoozabadi Z, Teimoori S, Chiti Z, *et al*. A comparison of the effect of levonorgestrel IUD with oral medroxyprogesterone acetate on abnormal uterine bleeding with simple endometrial hyperplasia and fertility preservation. Clinical and Experimental Obstetrics & Gynecology. 2013; 40: 421–424.
[61] Signorelli M, Caspani G, Bonazzi C, Chiappa V, Perego P, Mangioni C. Fertility-sparing treatment in young women with endometrial cancer or atypical complex hyperplasia: a prospective single-institution experience of 21 cases. BJOG: an International Journal of Obstetrics & Gynaecology. 2009; 116: 114–118. https://doi.org/10.1111/j.1471-0528.2008.02024.x
[62] El Behery MM, Saleh HS, Ibrahiem MA, Kamal EM, Kassem GA, Mohamed MES. Levonorgestrel-releasing intrauterine device versus dydrogesterone for management of endometrial hyperplasia without atypia. Reproductive Sciences (Thousand Oaks, Calif.). 2015; 22: 329–334. https://doi.org/10.1177/1933719114542014.
[63] Koskas M, Azria E, Walker F, Luton D, Madelenat P, Yazbeck C. Progestin treatment of atypical hyperplasia and well-differentiated adenocarcinoma of the endometrium to preserve fertility. Anticancer Research. 2012; 32: 1037–1043.
[64] Yu M, Yang J, Wu M, Lang J, Huo Z, Shen K. Fertility-preserving treatment in young women with well-differentiated endometrial carcinoma and severe atypical hyperplasia of endometrium. Fertility and Sterility. 2009; 92: 2122–2124. https://doi.org/10.1016/j.fertnstert.2009.06.013.
[65] Mentrikoski MJ, Shah AA, Hanley KZ, Atkins KA. Assessing Endometrial Hyperplasia and Carcinoma Treated with Progestin Therapy. American Journal of Clinical Pathology. 2012; 138: 524–534. https://doi.org/10.1309/AJCPM2TSDDF1MHBZ.
[66] Chen M, Jin Y, Li Y, Bi Y, Shan Y, Pan L. Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer. International Journal of Gynaecology and Obstetrics: the Official Organ of the International Federation of Gynaecology and Obstetrics. 2016; 132: 34–38. https://doi.org/10.1016/j.ijgo.2015.06.046.
[67] Mitsuhashi A, Sato Y, Kiyokawa T, Koshizaka M, Hanaoka H, Shozu M. Phase II study of medroxyprogesterone acetate plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2016; 27: 262–266. https://doi.org/10.1093/annonc/mdv539.
[68] Ismail MT, Fahmy DM, Elshmaa NS. Efficacy of levonorgestrel-releasing intrauterine system versus oral progestins in treatment of simple endometrial hyperplasia without atypia. Reproductive Sciences (Thousand Oaks, Calif.). 2013; 20: 45–50. https://doi.org/10.1177/1933719112459243.
[69] Ozdegirmenci O, Kayikcioglu F, Bozkurt U, Akgul MA, Haberal A. Comparison of the efficacy of three progestins in the treatment of simple endometrial hyperplasia without atypia. Gynecologic and Obstetric Investigation. 2011; 72: 10–14. https://doi.org/10.1159/000321390.
[70] Pashov AI, Tskhay VB, Ionouchene SV. The combined GnRH-agonist and intrauterine levonorgestrel-releasing system treatment of complicated atypical hyperplasia and endometrial cancer: a pilot study. Gynecological Endocrinology. 2012; 28: 559–561. https://doi.org/10.3109/09513590.2011.649813.
[71] De Marzi P, Bergamini A, Luchini S, Petrone M, Taccagni GL, Mangili G, *et al*. Hysteroscopic Resection in Fertility-Sparing Surgery for Atypical Hyperplasia and Endometrial Cancer: Safety and Efficacy. Journal of Minimally Invasive Gynecology. 2015; 22: 1178–1182. https://doi.org/10.1016/j.jmig.2015.06.004.
[72] Giampaolino P, Di Spiezio Sardo A, Mollo A, Raffone A, Travaglino A, Boccellino A, *et al*. Hysteroscopic Endometrial Focal Resection followed by Levonorgestrel Intrauterine Device Insertion as a Fertility-Sparing Treatment of Atypical Endometrial Hyperplasia and Early Endometrial Cancer: A Retrospective Study. Journal of Minimally Invasive Gynecology. 2019; 26: 648–656. https://doi.org/10.1016/j.jmig.2018.07.001.
[73] Tamauchi S, Kajiyama H, Utsumi F, Suzuki S, Niimi K, Sakata J, *et al*. Efficacy of medroxyprogesterone acetate treatment and re-treatment for atypical endometrial hyperplasia and endometrial cancer. The Journal of Obstetrics and Gynaecology Research. 2018; 44: 151–156. https://doi.org/10.1111/jog.13473.
[74] Lee SY, Kim MK, Park H, Yoon BS, Seong SJ, Kang JH, *et al*. The effectiveness of levonorgestrel releasing intrauterine system in the treatment of endometrial hyperplasia in Korean women. Journal of Gynecologic Oncology. 2010; 21: 102. https://doi.org/10.3802/jgo.2010.21.2.102.
[75] Shan B, Ren Y, Sun J, Tu X, Jiang Z, Ju X, *et al*. A prospective study of fertility-sparing treatment with megestrol acetate following hysteroscopic curettage for well-differentiated endometrioid carcinoma and atypical hyperplasia in young women. Archives of Gynecology and Obstetrics. 2013; 288: 1115–1123. https://doi.org/10.1007/s00404-013-2826-8
[76] Pronin SM, Novikova OV, Andreeva JY, Novikova EG. Fertility-Sparing Treatment of Early Endometrial Cancer and Complex Atypical Hyperplasia in Young Women of Childbearing Potential. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 2015; 25: 1010–1014. https://doi.org/10.1097/IGC.0000000000000467.
[77] Acosta-Torres S, Murdock T, Matsuno R, Beavis AL, Stone RL, Wethington SL, *et al*. The addition of metformin to progestin therapy in the fertility-sparing treatment of women with atypical hyperplasia/endometrial intraepithelial neoplasia or endometrial cancer: Little impact on response and low live-birth rates. Gynecologic Oncology. 2020; 157: 348–356. https://doi.org/10.1016/j.ygyno.2020.02.008.
[78] Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. Obstetrics & Gynecology. 1997; 90: 434–440. https://doi.org/10.1016/s0029-7844(97)00297-4.
[79] Leone Roberti Maggiore U, Martinelli F, Dondi G, Bogani G, Chiappa V, Evangelista MT, *et al*. Efficacy and fertility outcomes of levonorgestrel-releasing intra-uterine system treatment for patients with atypical complex hyperplasia or endometrial cancer: a retrospective study. Journal of Gynecologic Oncology. 2019; 30: e57. https://doi.org/10.3802/jgo.2019.30.e57.
[80] Shan W, Wang C, Zhang Z, Gu C, Ning C, Luo X, *et al*. Conservative therapy with metformin plus megestrol acetate for endometrial atypical hyperplasia. Journal of Gynecologic Oncology. 2014; 25: 214. https://doi.org/10.3802/jgo.2014.25.3.214.
[81] Wheeler DT, Bristow RE, Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. American Journal of Surgical Pathology. 2007; 31: 988–998. https://doi.org/10.1097/PAS.0b013e31802d68ce.
[82] Yang YF, Liao YY, Liu XL, Su SG, Li LZ, Peng NF. Prognostic factors of regression and relapse of complex atypical hyperplasia and well-differentiated endometrioid carcinoma with conservative treatment. Gynecologic Oncology. 2015; 139: 419–423.

https://doi.org/10.1016/j.ygyno.2015.10.015.
[83] Zhou R, Yang Y, Lu Q, Wang J, Miao Y, Wang S, *et al*. Prognostic factors of oncological and reproductive outcomes in fertility-sparing treatment of complex atypical hyperplasia and low-grade endometrial cancer using oral progestin in Chinese patients. Gynecologic Oncology. 2015; 139: 424–428. https://doi.org/10.1016/j.ygyno.2015.09.078.
[84] Madeddu C, Macciò A, Panzone F, Tanca FM, Mantovani G. Medroxyprogesterone acetate in the management of cancer cachexia. Expert Opinion on Pharmacotherapy. 2009; 10: 1359–1366. https://doi.org/10.1517/14656560902960162.
[85] Patseadou M, Michala L. Usage of the levonorgestrel-releasing intrauterine system (LNG-IUS) in adolescence: what is the evidence so far? Archives of Gynecology and Obstetrics. 2017; 295: 529–541. https://doi.org/10.1007/s00404-016-4261-0.
[86] Auclair MH, Yong PJ, Salvador S, Thurston J, Colgan TTJ, Sebastianelli A. Guideline No. 390-Classification and Management of Endometrial Hyperplasia. Journal of Obstetrics and Gynaecology Canada: JOGC = Journal D'obstetrique et Gynecologie du Canada: JOGC. 2019; 41: 1789–1800. https://doi.org/10.1016/j.jogc.2019.03.025.
[87] Uccella S, Zorzato PC, Dababou S, Bosco M, Torella M, Braga A, *et al*. Conservative Management of Atypical Endometrial Hyperplasia and Early Endometrial Cancer in Childbearing Age Women. Medicina (Kaunas, Lithuania). 2022; 58: 1256. https://doi.org/10.3390/medicina58091256.
[88] WHO Guidelines Approved by the Guidelines Review Committee. Medical Eligibility Criteria for Contraceptive Use. World Health Organization: Geneva. Copyright © World Health Organization 2015. Available at: https://www.who.int/publications/i/item/9789241549158. (Accessed: 1 December 2024).
[89] Tepper NK, Krashin JW, Curtis KM, Cox S, Whiteman MK. Update to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2016: Revised Recommendations for the Use of Hormonal Contraception Among Women at High Risk for HIV Infection. MMWR. Morbidity and Mortality Weekly Report. 2017; 66: 990–994. https://doi.org/10.15585/mmwr.mm6637a6.
[90] Chu MC, Zhang X, Gentzschein E, Stanczyk FZ, Lobo RA. Formation of ethinyl estradiol in women during treatment with norethindrone acetate. The Journal of Clinical Endocrinology and Metabolism. 2007; 92: 2205–2207. https://doi.org/10.1210/jc.2007-0044.
[91] Kuhnz W, Heuner A, Hümpel M, Seifert W, Michaelis K. In vivo conversion of norethisterone and norethisterone acetate to ethinyl etradiol in postmenopausal women. Contraception. 1997; 56: 379–385. https://doi.org/10.1016/s0010-7824(97)00174-1.
[92] Huvinen E, Holopainen E, Heikinheimo O. Norethisterone and its acetate - what's so special about them? BMJ Sexual & Reproductive Health. 2021; 47: 102–109. https://doi.org/10.1136/bmjsrh-2020-200619.
[93] Dow ML, Szymanski LM. Effects of Overweight and Obesity in Pregnancy on Health of the Offspring. Endocrinology and Metabolism Clinics of North America. 2020; 49: 251–263. https://doi.org/10.1016/j.ecl.2020.02.005.
[94] Helle E, Priest JR. Maternal Obesity and Diabetes Mellitus as Risk Factors for Congenital Heart Disease in the Offspring. Journal of the American Heart Association. 2020; 9: e011541. https://doi.org/10.1161/JAHA.119.011541.
[95] Wang C, Wu W, Yang H, Ye Z, Zhao Y, Liu J, *et al*. Mendelian randomization analyses for PCOS: evidence, opportunities, and challenges. Trends in Genetics: TIG. 2022; 38: 468–482. https://doi.org/10.1016/j.tig.2022.01.005.
[96] Puttabyatappa M, Cardoso RC, Padmanabhan V. Effect of maternal PCOS and PCOS-like phenotype on the offspring's health. Molecular and Cellular Endocrinology. 2016; 435: 29–39. https://doi.org/10.1016/j.mce.2015.11.030.