Systematic Review and Meta-Analysis

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Fertility-preserving treatment in patients with early-stage endometrial cancer

A protocol for systematic review and meta-analysis

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Abstract

Background: Endometrial cancer (EC) is the second most common malignancy of the female reproductive system worldwide, and the standard treatment for early-stage EC potentially leads to permanent infertility. The objective of this study was to investigate the efficacies of different methods on fertility preservation in patients with early-stage EC.

Methods: We searched the major online databases (PubMed, Embase, The Cochrane Library, and Web of Science) to collect the research literature on fertility preservation therapy in patients with early-stage well-differentiated EC aged ≤ 40 years from January 1999 to October 2019. The inclusion was performed using the R software (version R3.5.3) meta-analysis of a single rate. The efficacy of the following three fertility preservation treatments was evaluated from four aspects, the complete remission rate (CRR), recurrence rate (ReR), pregnancy rate (PregR), and live birth rate (LBR): a) taking oral progestin only therapy, b) hysteroscopic resection combined with progestin/levonorgestrel-releasing intrauterine system (LNG-IUS)/GnRH-a, c) LNG-IUS or combined with progestin/GnRH-a.

Results: A total of 23 articles were included in this study, including 446 patients with early-stage EC. In the group that took oral progestin only (n = 279), CRR, ReR, PregR, and LBR were 82% (95% confidence interval [CI], 74%–92%, $P = .01$), 38% (95% CI, 31%-45%, $P = .35$), 70% (95% CI, 62%–79%, $P = .68$), and 63% (95% CI, 55%–73%, $P = .55$), respectively. Hysteroscopic resection combined with progestin/LNG-IUS/GnRH-a therapy group (n = 96) achieved a CRR, ReR, PregR, and LBR of 95% (95% CI, 90%–100%, $P = .42$), 16% (95% CI, 6%–39%, $P = .03$), 84% (95% CI, 73%–96%, $P = .39$), and 72% (95% CI, 59%–87%, $P = .28$), respectively. LNG-IUS or combined with progestin/GnRH-a therapy group (n = 91) achieved a CRR, ReR, PregR, and LBR of 69% (95% CI, 54%–89%, $P < .01$), 30% (95% CI, 19%–49%, $P = .36$), 48% (95% CI, 18%–100%, $P < .01$), and 36% (95% CI, 10%–100%, $P < .01$), respectively.

Conclusion: It is safe and effective for young patients with early-stage EC to receive oral progestin, hysteroscopic resection combined with progestin/LNG-IUS/GnRH-a, LNG-IUS, or progestin/GnRH-a.

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Abbreviations: 95%CI = 95% confidence interval, CRR = complete remission rate, EC = endometrial cancer, LBR = live birth rate, LNG-IUS = levonorgestrel-releasing intrauterine system, PregR = pregnancy rate, ReR = recurrence rate.

Keywords: endometrial cancer, fertility preservation, hysteroscopic resection, levonorgestrel-releasing intrauterine system, progestin

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Ethical approval. The data used in this meta-analysis were collected from published studies, therefore, ethical approval was waived.

Compliance with ethical standards

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

Endometrial cancer (EC) is the second most common malignancy of the female reproductive system worldwide, second only to cervical cancer,[1] and its incidence is gradually increasing each year. It typically attacks young women,[2] and approximately 25% of patients develop EC before menopausal, 10% of whom are younger than 40 years old and approximately 80% have type I EC (estrogen-dependent).[3] The standard treatment for patients with early-stage EC is total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy.[4] Despite a higher 5-year survival rate (more than 90%),[5] it permanently deprives patients of their fertility. Due to late marriage and late childbearing, the universal two-child policy and other factors, an increasing number of young women are eager to retain reproductive function. Therefore, it is of vital importance to preserve reproductive function in the treatment of early-stage EC in young patients.

2. Materials and methods

2.1. Date sources and searches

We searched the PubMed, Embase, Cochrane Library, and Web of Science databases for English language articles published from January 1999 to October 2019, involving all fertility-preserving treatments for young patients with grade 1 presumed stage IA EC. We combined medical subject headings with a keyword search. For each database, we retrieved five keywo**rds: EC, fertility preservation, hysteroscopic resection, progesterone, levonorgestrel-releasing intrauterine system (LNG-IUS), and their related words, and formed a retrieval mode for retrieval.

2.2. Study selection

EC patients included in this study should meet the following requirements: a) women aged $\leq$40 years who had a strong desire to preserve their reproductive function; b) histopathologically confirmed well-differentiated endometrial adenocarcinoma; c) no myometrium infiltration and involvement of cervical parenchyma detected and no paracasal metastasis detected by transvaginal ultrasonography or magnetic resonance imaging; d) positive progesterone receptors; and e) no medication contraindications for progesterone. The exclusion criteria were as follows: a) single case report and case reports involving less than five cases and b) articles in academic conferences, literature with incomplete original data or without an exact number of cases, and research literature with a quality evaluation score of less than 8; c) published literature with duplicate data.

2.3. Data extraction

The extracted data included the following aspects: a) basic information of the included study: title, author and contact information, year of publication, time of research, country; b) basic characteristics of the research subjects: research type, age of subjects, and specific interventions; c) risk of bias assessment included in the study and quality assessment; d) main data of associated outcome indicators: total number of samples, number of remission, number of recurrences, number of pregnancies, number of pregnancies, number of births, pregnancy pattern, remission time, recurrence time, and follow-up time; and outcome measurement parameters: complete remission rate (CRR), recurrence rate (ReR), pregnancy rate (PregR), and live birth rate (LBR).

2.4. Quality control

In this process, two researchers independently screened the literature, and extracted and cross-checked the data. Any disagreement was resolved through discussion or judged by a third researcher.

2.5. Statistical analysis

In this study, the R3.5.3 software was used for a meta-analysis of single rate. The heterogeneity test included in the study was evaluated using Q-value statistics and a forest map. As for heterogeneity test results, $P > .1$ suggested homogeneity in multiple studies, while $P \leq .1$ suggested heterogeneity of multiple studies; heterogeneity was measured by I^2; $I^2 = 25\%$ indicated mild heterogeneity; $I^2 = 50\%$ indicated moderate heterogeneity; and $I^2 = 75\%$ indicated high heterogeneity. In this study, when $I^2 < 50\%$, the fixed effect model was used for meta-analysis; if $I^2 \geq 50\%$, the causes of heterogeneity needed to be analyzed, and the resulting heterogeneity was calculated by subgroup analysis. If the causes of heterogeneity could not be distinguished, a random-effects model was used for meta-analysis. Finally, the results were displayed as a forest map. Publication bias was assessed using a funnel plot.

3. Results

This study included 23 articles that fulfilled the selection criteria (Fig. 1), involving 466 patients with early-stage EC, including 11 articles on oral progestin therapy involving 213 patients that were treated, 7 articles on hysteroscopic resection combined with progestin/LNG-IUS/GnRH-a therapy involving 96 patients, and 5 articles on LNG-IUS or combined with progestin/GnRH-a therapy involving 91 patients. The type of research in this study included case analysis and cohort studies. The 1–8 Items of the MINORS scale were used for quality evaluation, and all the scores of the literature included were $\geq$ 8. The basic characteristics and three conservative treatments included in the literature are listed in Tables 1 and 2.

3.1. Taking oral progestin only therapy

There were 11 references with a total number of 279 presumed early-stage EC patients who received oral progestin therapy. Pathological CR was achieved in 75.3% (213/279) of the patients. All data were imported into R3.5.3. The P value for the heterogeneity X^2 test was 0.01, with $I^2 = 56\%$, indicating moderate heterogeneity among the studies. We could not determine the source of heterogeneity and used the random effects model to analyze and interpret the results of statistical analysis, with a pooled CRR of 82% (95% confidence interval [95%CI], 74%-92%). Of the CR patients, 32.7% (69/211) experienced recurrence after remission. The P-value for the heterogeneity X^2 test was 0.35, with $I^2 = 10\%$, and the results were homogeneous. A fixed effect model was used for meta-analysis, with a pooled ReR of 38% (95% CI, 31%-45%). Among the 115 patients who achieved CR, 73 were preparing themselves for immediate pregnancy, and subsequently, 63.5% (73/115) of the patients became pregnant. The P-value for the heterogeneity X^2 test was 0.68, with $I^2 = 0$, and the results were

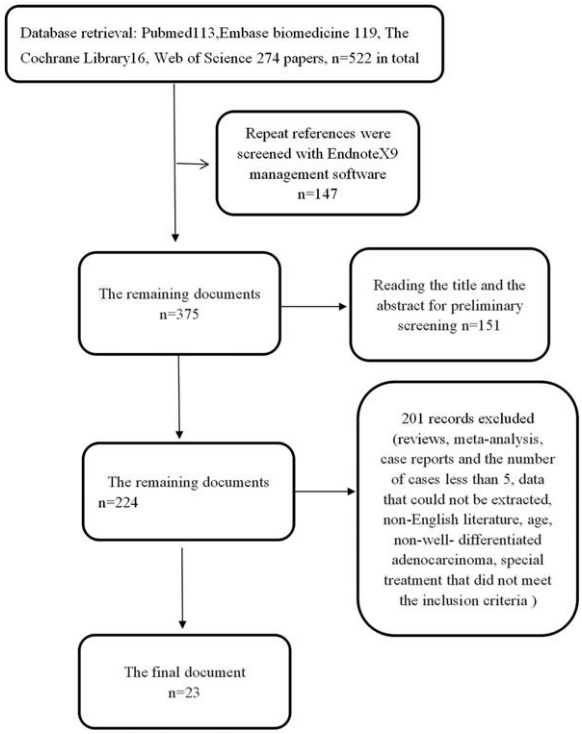

Figure 1. Literature screening.

homogeneous. A fixed effect model was used for analysis, with a pooled PregR of 70% (95% CI, 62%-79%). A total of 63.5% (62/109) of the patients delivered babies. The *P*-value for the heterogeneity X^2 test was 0.55, with $I^2=0$, and the results were homogeneous. A fixed-effect model was used for analysis, with a pooled LBR of 63% (95% CI, 55%-73%) (Fig. 2).

3.2. Hysteroscopic resection combined with progestin /LNG-IUS/ GnRH-a/Therapy

There were seven references with a total of 96 presumed early-stage EC patients who underwent hysteroscopic resection. Pathological CR was achieved in 90.6% (87/96) of the patients. All data were imported into the R3.5.3 statistical software. The *P*-value for the heterogeneity X^2 test was 0.42, with $I^2=0$, and the results were homogeneous. A fixed-effect model was used for analysis, with a pooled CRR of 95% (95%CI, 90%-100%). Of the CR patients, 20.7% (18/87) experienced recurrence after remission. The *P*-value for the heterogeneity X^2 test was 0.03, with $I^2=58\%$, indicating moderate heterogeneity among the studies. We could not determine the source of heterogeneity, and the random effects model was used to analyze and interpret the results of statistical analysis, with a pooled ReR of 16% (95% CI, 6%-39%). Among the 46 patients who achieved CR, 32 prepared themselves for immediate pregnancy, and 69.6% (32/46) were pregnant. The *P*-value for the heterogeneity X^2 test was 0.39, with $I^2=5\%$. The results were homogeneous, and a fixed-effect model analysis was performed, with a pooled PregR of 84%

Table 1

Basic characteristics of 23 studies.

Study	Year	No. Total	Age (Range)(yr)	Treatment Methods (mg/d)	Follow-UP Medial (range)(mo)	Outcome	Minors (Total score 16)
Gotlieb, W. H. (2003)[6]	1970 -2000	10	23-40	MA (160) or OH-prog. 3g qw or Norethisterone acetate (5)	82 (6–358)	One death, The others NED (The patient died of coronary heart disease 17 years after surgery)	13
Yuh-Cheng Yang. (2005)[7]	1993-2004	6	27-39	MA (160)	48.8 (14–132)	NED	13
Ushijima, K. (2007)[8]	—	22	2-39	MPA (600)+ aspirin (81)	47.9 (25–73)	_	13
Yamazawa, K. (2007)[9]	1999-2005	9	28-40	MPA (400)	35 (24–69)	NED	13
Signorelli, M. (2009)[10]	1992–2009	11	<40	Natural progestin 200mg*(14–25d)	98 (35–176)	NED	13
Yu, M. (2009)[11]	1991-2005	8	≤35	MPA (250–500)	31.8 (5–90)	NED	14
Mao, Y. (2010)[12]	2001–2009	6	26-31	MPA (250or 500)or MA (160)	50 (32–77)	NED	12
Koskas, M. (2012)[13]	2001-2010	8	28-38	MA (10 or160) or MPA (10) or NA or Lynestrenol (15)	44.5 (17–86)	NED	14
Park, H. (2012)[14]	2000-2008	14	21-38	MPA (250 or 500) or MA (30or160 or240)	35.5 (18–135)	NED	13
Park, J.Y. (2013)[15]	1996-2011	177	<40	MPA (30–1500)or MA (40–240)	66 (14–196)	NED	12
Shobeiri, M. J. (2013)[16]	2002-2011	8	24-35	MA (320) or MA (320)+GnRH-a	34.5 (11–72)	NED	13
Mazzon, I. (2010)[17]	2007-2011	6	26-38	HR+ MA (160)	50.5 (21–82)	NED	14
Laurelli, G. (2011)[18]	2002-2008	14	26-40	HR+MA (160) / LNG-IUD	40 (13–79)	NED	13
Wang, c, J. (2014)[19]	1991-2010	37	18-40	HR+MA (160)+ tamoxifen (30)*8 weeks later/+ GnRH-a or anastrozole	78.6 (19.1–252.8)	1 AWD,others NED	13
Wang, Q. (2015)[20]	2006-2012	6	25-34	HR+MA (160)	48.5 (26–91)	NED	13
Laurelli, G. (2016)[21]	2006-2013	20	25-40	HR+LNG-IUD	85 (30–114)	NED	13
Tock, S. (2018)[5]	1999-2016	7	24-38	HR+ GnRH-a	15 (5–72)	NED	13
Yang, H. C. (2019)[22]	2013-2017	6	30-36	HR+(MPA500or MA160)	32 (4–49)	NED	13
Cade, T. J. (2010)[23]	2012-2017	10	24-40	LNG-IUS	27 (3–134)	NED	13
Minig, L. (2011)[24]	2008-2012	14	20-40	LNG-IUS+GnRH-a	27-70	NED	12
Kim, M. K. (2013)[25]	2012-2017	16	29–40	MPA500+LNG-IUS	2 8 (16–50)	NED	11
Kim, M. K. (2019)[26]	2004-2017	35	27-40	MPA (500)+ LNG-IUS	6	CR 13, PR 9, NC 13	12
Maggiore, U. L.R (2019).[27]	1996-2009	16	33.4±5.0	LNG-IUS	85.3±48.3	_	12

AWD = alive with disease, BID = bis in die, CR = complete response, HR = hysteroscopic resection, MA = megestrol acetate, MPA = medroxyprogesterone acetate, NA = nomegestrol acetate, NC = no change, NED = no evidence of disease, OH-prog. = hydroxyprogesterone caproate, PR = partial response, QW = every week, TID = ter in die.

Table 2

Detailed data extracted from studies included.

Author, Year	Total	No. CR	No. Re	No. Prepared for Preg.	No. of Preg.	No. Birth	median (Re Time) (mo)	median (CR Time) (mo)	Type of Preg. (ART/Natural)
Treatment of onefold oral progestin									
Gotlieb, W. H. (2003)[6]	10	10	4	__	6	__	37 (19–357)	3.5 (2–8)	__
Yuh-Cheng Yang. (2005)[7]	6	4	2	4	2	2	4, 5	3.5 (2–5)	__
Ushijima,K. (2007)[8]	22	14	8	__	4	3	__	2–6.5	ART 2, N 1
Yamazawa,K. (2007)[9]	9	8	2	8	4	3	10, 22	6 (3–9)	ART
Signorelli, M. (2009)[10]	11	2	__	6	4	__	___	4 (1–7)	___
Yu, M. (2009)[11]	8	5	1	4	0	0	30	6.4 (3–10)	__
Mao,Y. (2010)[12]	6	4	0	4	3	3	0	7.5 (3–9)	ART 2, N 1
Koskas, M. (2012)[5,13]	8	5	2	5	2	2	12, 34	3 (3–6)	N
Park, H (2012)[14]	14	13	2	7	4	4	7-36	6 (3–15)	ART
Park,J.Y. (2013)[15]	177	141	45	70	51	46	17 (4–62)	18W* (8–55W)	ART 35, N 11
Shobeiri, M. J. (2013)[16]	8	7	3	7	3	2	18 (3–21)	6 (3–9)	ART 2
Treatment of hysteroscopic resection combined with progestin/LNG-IUS/GnRH-a									
Mazzon, I. (2010)[17,19]	6	6	0	6	4	4	0	3–9	N
Laurelli,G. (2011)[18]	14	14	1	3	1	1	5	__	N
Wang,c,J. (2014)[19]	37	30	15	11	8	4	20 (11–154)	4 (2–11)	__
Wang,Q. (2015)[20]	6	6	0	4	3	3	0	3	N
Laurelli,G. (2016)[21]	20	19	2	12	11	10	8, 41	6	ART 7, N 3
Tock,S. (2018)[5]	7	6	0	5	4	3	0	3.5 (3–6)	ART
Yang, H.C. (2019)[22]	6	6	0	5	1	1	0	6 (6–9)	N
Treatment of LNG-IUS or combined with progestin/GnRH-a									
Cade, T.J. (2010)[23]	10	8	0	__	__	__	__	5 (1–13)	__
Minig,L. (2011)[24]	14	8	2	8	1	1	16, 30	__	__
Kim, M.K. (2013)[25]	16	14	2	9	3	2	6, 7	9 (3–35)	ART
Maggiore, U.L.R. (2019)[27]	16	13	5	8	8	7	25.0±12.9	5.0±2.9	ART 6, N 1
Kim, M.K. (2019)[26]	35	13	__	__	__	__	__	6 (3–6)	__

W* = week, ART = assisted reproduction technology, N = natural.

(95% CI, 73%-96%). A total of 54.3% (25/46) of the patients delivered babies. The *P*-value for the heterogeneity X^2 test was .28. with $I^2=20$. The results were homogeneous, and a fixed-effect model analysis was performed with a pooled LBR of 72% (95% CI, 59%-87%) (Fig. 3).

3.3. The LNG-IUS or combined with Progestin/GnRH-a therapy

There were five references in the literature, with a total of 91 patients receiving LNG-IUS or combined progestin/GnRH-a therapy. CR was achieved in 61.5% (56/91) of the patients. All data were imported into the R3.5.3 statistical software. The *P*-value for the heterogeneity X^2 test was less than 0.01, with $I^2=$ 73%, indicating moderate heterogeneity among the studies. The random effect model was used to analyze and interpret the statistical results, with a pooled CRR of 69% (95% CI, 54%-89%). Of the CR patients, 20.9% (9/43) experienced recurrence after remission, and the *P*-value for the heterogeneity X^2 test was 0.36, with $I^2=6\%$. The results were homogeneous, and a fixed-effect model analysis was performed, with a pooled ReR of 30% (95%CI,19–49%). There were 25 patients preparing themselves for immediate pregnancy, and 44% (11/25) of the patients became pregnant. The *P*-value for the heterogeneity X^2 test was less than 0.01, with $I^2=81\%$, and the results were highly heterogeneous. The random effect model analysis was performed with a pooled PregR of 48% (95% CI, 8%-100%). A total of 40% (10/25) of the patients delivered babies. The *P*-value for the heterogeneity X^2 test was 0.01, with $I^2=77\%$, which was highly heterogeneous. The random effect model analysis was performed with a pooled LBR of 36% (95% CI, 10–100%) (Fig. 4).

3.4. Risk of publication bias

Computer-based retrieval was used in this study, in addition to manual retrieval and gray literature retrieval. In the meantime, incomplete data in the studies included and a large number of studies excluded might have introduced publication bias.

At least 10 studies were needed to draw the funnel diagram, because the number of studies included was too small to detect asymmetry in funnel plots. In this study, the LNG-IUS and hysteroscopic resection groups did not draw a funnel chart due to the small number of studies, which might have led to publication bias.

It was evident that the funnel plot was relatively symmetrical, indicating no obvious publication bias in different oral progestin groups, except in the CR group. We analyzed the results of the group taking oral progesterone only and found a significant difference between the patients who periodically took oral natural progesterone. The heterogeneity decreased significantly after recalculation, and CR was achieved in 78.7% (211/268) of the patients. The *P*-value for the heterogeneity X^2 test was .05, with $I^2=47\%$, and a fixed-effect model analysis was performed, with a pooled CRR of 84% (95%CI, 80%-89%) (Fig. 5).

4. Discussion

4.1. Information on taking oral progestin only therapy

In this study,[6–16] progestin therapy contained a variety of progestin types such as MPA, MA, D, norethindrone acetate lynestrenol, and natural progesterone. The species and doses

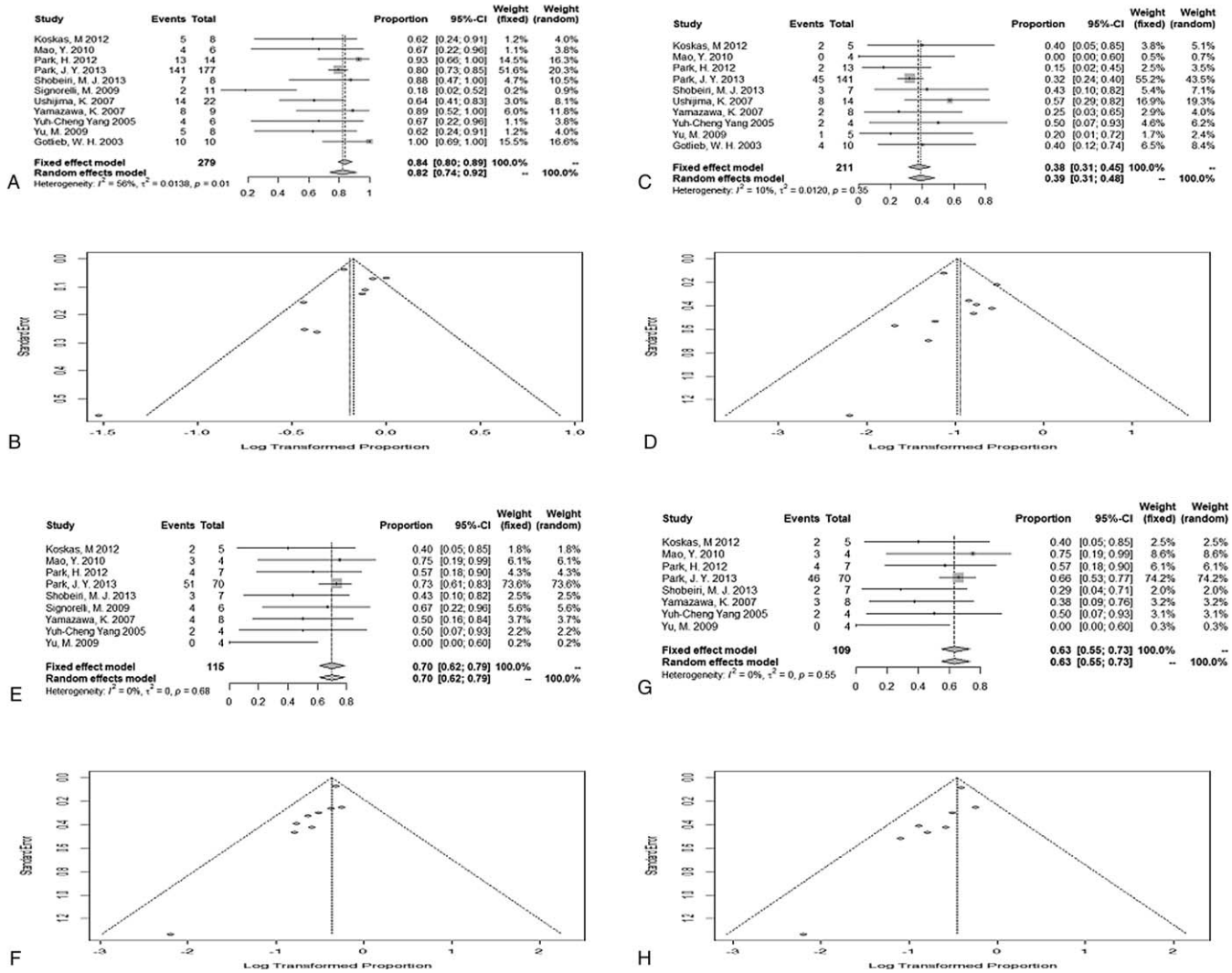

Figure 2. Forest and funnel plots of CRR, ReR, PregR and LBR for oral progestin. A, B, Forest and funnel plots of CRR. C, D, Forest and funnel plots of ReR. E, F, Forest and funnel plots of PregR, G, H Forest and funnel plots of LBR.

(MPA range, 10–1500 mg/d; MA range, 30–320 mg/d), duration of treatment (range,1–15 months), and follow-up time (range, 5–358 months) varied greatly. In this study,[12] we found that the most common adverse effects for oral progestin were weight gain and damage to liver function; 213 patients achieved CR, with a remission time (range, 1–15 months), of which there were 69 patients who recurred, with a recurrence time of 1–26 months, as shown in 25 articles by Qin Yun et al.[28] In a meta-analysis of oral progesterone in the treatment of early-stage EC, CR was reported to be 82.4% (95% CI, 75.3%-88.7%), and the ReR was 25.0% (95% CI, 15.8%-35.2%). The remission rate was higher, but the ReR was lower than that reported in the literature.

4.2. Information on hysteroscopic resection combined with Progestin/LNG-IUS/GnRH-a therapy

Hysteroscopic resection in this study referred to the resection of the tumor lesion, its adjacent endometrium, and the superficial myometrium under the lesion. Among the 68 patients who underwent hysteroscopic resection followed by progestin/GnRH-a therapy, 28 underwent LNG-IUS placement after hysteroscopic resection. Among them, 87 patients achieved CR, with a remission time of 2 to 11 months, including 18 patients who experienced recurrence. Time to recurrence (range, 11–154 months) and follow-up time (range, 4–252.8 months). Hysteroscopic resection was preferable in patients with limited lesions. If the lesion was extensive, a large amount of endometrial tissue should be removed. It could cause obvious morphologcal changess of the uterine cavity or serious adhesion of the uterine cavity, thus affecting the postoperative pregnancy; therefore, conservative treatment would be ineffective.[20,29]

4.3. Information on LNG-IUS combined with Progestin/GnRH-a therapy

This study included a levonorgestrel sustained-release system or a combination of progestin/GnRH-a treatment. There were five articles in total, in which 91 patients were treated. Of them, 26 patients in two articles were treated with LNG-IUS alone, 51 patients in two articles were treated with LNG-IUS combined

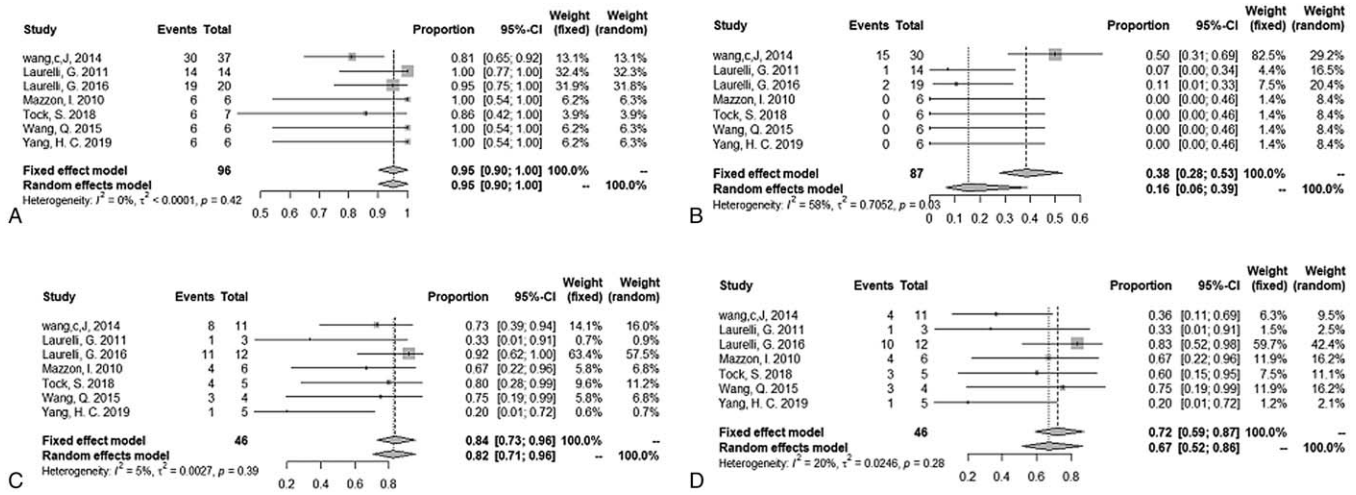

Figure 3. Forest plots of meta-analysis of CRR, ReR, PregR, and LBR for hysteroscopic resection followed by progestin/GnRH-a/LNG-IUS therapy. A, forest plot of CRR; B, forest plot of ReR; C, forest plot of PregR; D, forest plot of LBR.

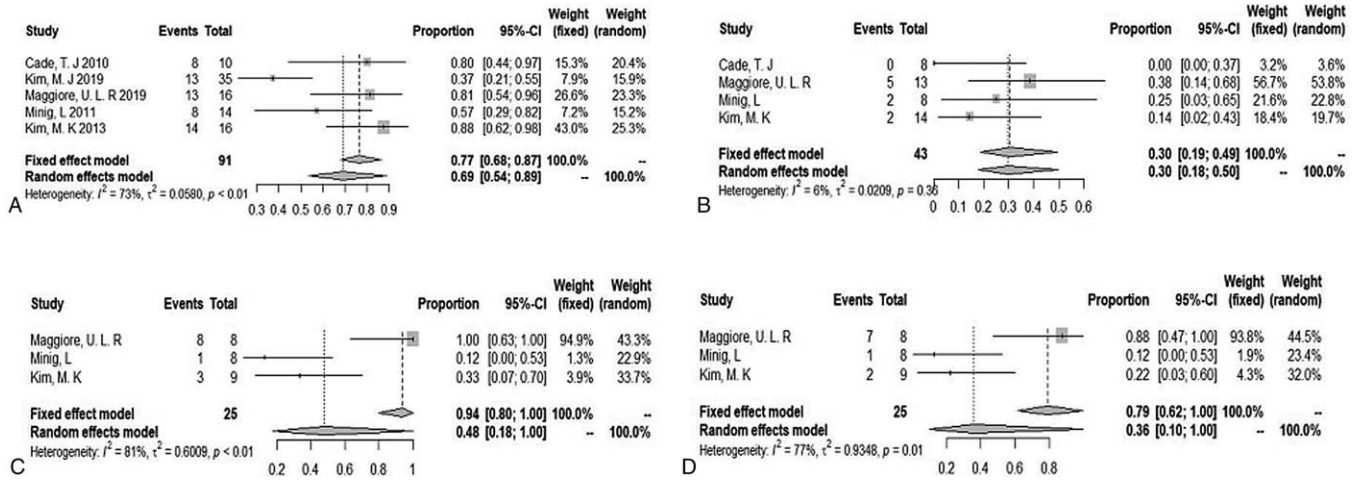

Figure 4. Forest plots of meta-analysis of CRR, ReR, PregR, and LBR for the LNG-IUS combined with GnRH-a/progestin therapy. A, forest plot of CRR; B, forest plot of ReR; C, forest plot of PregR; D, forest plot of LBR.

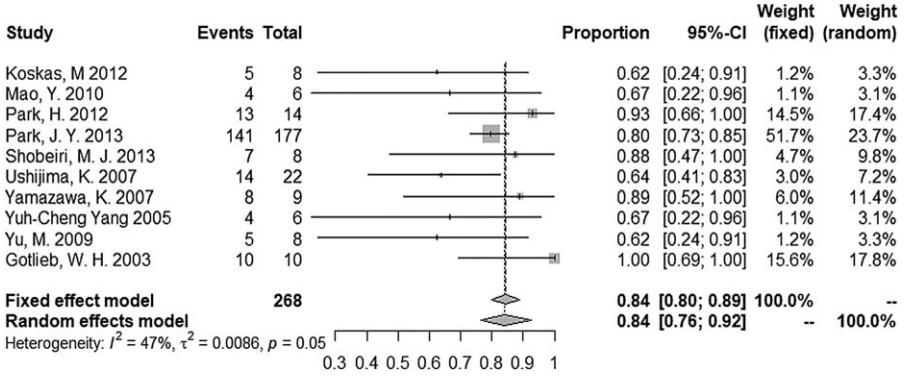

Figure 5. Forest and funnel plots of CRR for oral progestin.

with MPA 500 mg/d, progestin 200 to 400 mg/d, and 14 patients in one article were treated with LNG-IUS combined with GnRH-a3.75 mg/28 d. The remission time ranged from 1 month to 35 months, and the time to recurrence ranged from 6 months to 30 months. The results of the statistical analysis showed 91 patients with early-stage EC, CRR of 69% (95% CI, 54%-89%), and ReR of 30% (95%CI, 19%-49%). Fan ZP reported on six young patients with early-stage EC.[30] In a meta-analysis of progesterone or GnRH-a therapy, 72.9% (95%CI, 60.4%-82.5%) of patients reported complete remission, with a ReR of 11% (95% CI, 5.1%-22.0%). CRR was significantly higher, but the ReR was lower than that in the present study. The application of LNG-IUS in patients with early-stage EC could reduce adverse reactions caused by long-term high-dose oral progesterone therapy, with good compliance. However, few studies have reported the application of LNG-IUS in early-stage EC to date. Some of the literature included in this study had a short follow-up time,[26] resulting in some publication bias. In the future, a large sample control study is needed to provide a better basis for clinical application. In this study, the symptoms of nine patients were partially relieved, as compared to 13 patients who were not. Due to insufficient follow-up, no further treatment was reported,[26] and disease-free survival was reported in other studies.

4.4. Comparison of the 3 Methods in CRR, ReR, PregR and LBR

In this study, the CRRs for the oral progestin group, HR followed by progestin/GnRH-a/LNG-IUS group, and LNG-IUS or combined with GnRH-a/progestin groups were 82%, 95%, and 69%, respectively. ReR was 38%, 16%, 30%, PregR was 70%, 84%, 48%, and LBR was 63%, 72%, 36%, respectively. The HR group achieved the highest CRR, PregR, LBR, and the lowest ReR. It might be associated with more complete hysteroscopic resection of the lesion, higher postoperative remission rate, and postoperative adjuvant progesterone therapy, which reduced the postoperative ReR. The CRR and ReR were higher in the progesterone group than in the LNG-IUS group. Systemic adverse reactions caused by the oral administration of high-dose progesterone were higher than those with LNG-IUS. Therefore, conservative treatment methods should be individualized according to the patient's condition.

In a conservative treatment of 146 cases of early-stage EC in a randomized controlled study by Yao J,[31] hysteroscopic conservative surgery with progesterone therapy, as compared with oral progesterone alone, led to a higher total effective rate (95.89% vs. 69.86%) and total pregnancy rates (93.15% vs. 67.12%), but a lower total ReR (6.85% vs. 31.51%), suggesting significant differences. In a meta-analysis by Fan ZP, an indirect comparison (taking oral progestin-only therapy; hysteroscopic resection followed by progestin therapy; LNG-IUS or combined with progestin/GnRH-a) showed that hysteroscopic resection followed by progestin therapy had the highest CRR (95.3%), and ReR (30.7%) was the highest in the oral progestin-only therapy. These findings were generally consistent with the results of conservative treatment in this meta-analysis that hysteroscopic resection combined with other treatment methods was more effective. However, large randomized controlled studies comparing the efficacy of different conservative treatments will be needed for further confirmation.

5. Conclusions

1. It is safe and effective for young patients with early-stage EC to receive oral progestin, hysteroscopic resection combined with progestin/LNG-IUS/GnRH-a, LNG-IUS, or progestin/GnRH-a.
2. Any kind of conservative treatment may contribute to recurrence, therefore, long-term follow-up will be needed. Future randomized controlled studies with large samples are needed to compare the efficacy of different conservative treatment methods to select the optimal option.

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