Gynecologic Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Updates on conservative management of endometrial cancer in patients younger than 45 years

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HIGHLIGHTS

- Fertility-sparing treatment for endometrial cancer is challenging.
- It is the review with the largest number of patients with endometrial cancer.
- There is a lower rate of hysterectomies with endometrial resection.
- More pregnancies are achieved.

ARTICLE INFO

Article history:
Received 17 February 2021
Accepted 12 April 2021
Available online xxxx

Keywords:
Endometrial cancer
Fertility sparing treatment
Hormonal treatment
Surgical treatment
Endoscopic resection
Uterine malignancy

ABSTRACT

Endometrial cancer is the most common gynecologic malignancy in developed country. Women under the age of 40 represent 5% of all endometrial cancer and the majority are nulliparous at the time of diagnosis. The aim of this review was to compare oncologic and fertility outcomes among different fertility-preserving therapies in patients under 45 years of age with grade 1 or 2 endometrial cancer.

A systematic review was conducted, the MEDLINE, EMBASE, and CINAHL databases were searched for articles published during the period from January 2010 through January 2020 in accordance with PRISMA guidelines, using the terms endometrial cancer, fertility sparing treatment and conservative treatment.

A total of 661 patients in 38 studies were included. The median age was 32.3 years (range 13-–43). Regardless of the primary treatment, it is always accompanied by systemic or local hormonal treatment. The median follow-up time was 47.92 months (range 1–412), 54.9 months (range 3.4–412) for the progesterone group, 38.97 months (range 3–172) for the hysteroscopic resection group and 23.11 months (range 1–115.5) for the Levonorgestrel Intrauterine Device group. The overall complete response rate was 79.4%, [Hysteroscopic Resection: 90%, hormonal treatment: 77.7%, and Levonorgestrel Intrauterine Device: 71.3%] The $p = 0.02$ when the primary treatment is Hysteroscopic resection, always followed by hormonal therapy either oral progesterone or Levonorgestrel Intrauterine Device. Patients who had tumor resection had lower progression than those who received hormonal treatment or Levonorgestrel Intrauterine Device 3.5% vs. 12.1% vs. 19.5% respectively ($p = 0.03$). The complete response time was higher in the Hysteroscopic Resection group ($p = 0.04$) with fewer patients undergoing hysterectomy ($p = 0.0001$). Patients who underwent Hysteroscopic Resection had higher pregnancy rates compared to medical treatment or Levonorgestrel Intrauterine Device, 34.5%, 27.6% and 18.4%, respectively ($p = 0.002$).

Conclusion. Patients who underwent Hysteroscopic Resection followed progestogens agent was associated to a better complete response, high pregnancy rates and minor numbers of hysterectomies.

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https://doi.org/10.1016/j.ygyno.2021.04.017
0090-8258/

Contents

1. Introduction

Endometrial cancer is the most common gynecologic cancer in developed country, with approximately 65,620 new cases expected in 2020 in United States, representing nearly 7% of all new cancer cases detected in women this year [1,2]. Although generally diagnosed in postmenopausal women, women under the age of 40 represent 5% of all endometrial cancer and the majority are nulliparous at the time of diagnosis [3,4]. When the cases arise in women of childbearing age, Endometrial Cancer usually presents favorable prognostic features consisting of endometrioid histology, 50%–60% have focal and well-differentiated (grade 1) lesions and about 80% absent or minimal myometrial invasion (stage I) [5–9].

The standard treatment for Endometrial Cancer consists of hysterectomy, bilateral salpingo-oophorectomy, and eventually pelvic and aortic lymphadenectomy [10]. This treatment precludes future fertility and may thus be undesirable to women wishing to maintain their reproductive potential. Given the excellent oncologic outcomes associated with early stage Endometrial Cancer, the importance of improving quality of life and preserving fertility-while maintaining excellent disease-free survival- has been recognized. Although fertility-sparing options for Endometrial Cancer management have increasingly been investigated, a contemporary consensus standardizing a conservative approach has not yet been defined.

The most studied fertility-preserving treatment for early endometrial cancer in young women is oral progestin therapy with a response rate range from 55% to 78% [11–13]. Recently, other options have been presented including the use of a hysteroscopically guided resection of the endometrial cancer followed by hormonal therapy and/or the use of intrauterine devices [14–16]. In this article, we aimed to compare oncologic and fertility outcomes among different fertility-preserving therapies in patients with grade 1 or 2 endometrial cancer who are 45 years of age and under.

1.1. Methods

We followed PRISMA guidelines to conduct a systematic review. The MEDLINE, EMBASE, and CINAHL databases were searched for articles published from January 2010 through January 2020 using the terms endometrial cancer, fertility sparing treatment and conservative treatment. Inclusion criteria consisted of articles describing stage of disease, surgical procedure, medical treatment, histological type and grade, pathologic complete response rate, fertility outcomes, site of recurrence and survival. Case reports and case series were included. Non-English language manuscripts, review articles or with duplicate patient information, articles that included patients over the age of 45, articles where it was not possible to separate if patients had atypical hyperplasia or endometrial cancer or those with non-traditional therapies were excluded. (Fig. 1).

Demographic data extracted from each study included: age, diagnosis, type of hormonal agent, method and timing of interval endometrial re-evaluation. Information concerning oncological outcomes were recorded including response rates, and particularly, percentage of women achieving a complete response, timing of complete response, number of women with complete response who later experienced a recurrence and those with a persistent or progressive disease. Although the definitions of complete response were different among the studies, we defined complete response as complete regression of atypia or carcinoma from 3 to 12 months follow-up, using specimens obtained via office-based endometrial biopsy, dilatation-curettage biopsy or hysteroscopic biopsy for the 3 treatment groups. Partial response was defined as the presence of atypical hyperplasia (AH) during the follow-up endometrial biopsy and persistent disease was defined if no evidence of disease regression was observed between 3 to 12 months to the corresponding treatment. Progression is defined as the appearance of grade 3 endometrial carcinoma. Time of response was measured as the date from the beginning of the corresponding treatment to complete response. Progressive disease, if higher than stage IA (according to 1988 staging system of The International Federation of Gynecology and Obstetrics [FIGO]) and/or the evolution of the histological stage from G1 to G2 or from G2 to G3 endometrial cancer, was diagnosed during follow-up. Recurrence was defined as the presence of Endometrial Cancer or Atypical Hyperplasia during follow-up after an endometrial sample showing disease regression. Data regarding reproductive outcomes was also collected including number of study subjects who became pregnant and number of live births; however, this information was not reported in eight articles.

Study quality was assessed utilizing a modified by Gunderson et al. [17] Newcastle–Ottawa Study Assessment Scale (Table 1), which emphasized the study design and ascertain outcomes based on follow-up length [18]. For calculations of median age and follow up times, individual data were used if the study reported these values. Otherwise, each subject in the study was assumed to be the reported mean or median value for the respective study. The quantitative variables were summarized expressed as means and standard deviation, while the qualitative variables were presented in percentages and absolute frequencies. To evaluate the outcomes of complete, partial, and progression, we used a cox proportional hazards model comparing each of the treatments [Oral Progestin, HR (always followed by hormonal therapy either oral progesterone or LNG-IUD) and LNG-IUD], thus calculating a HR with 95% confidence intervals. Finally, we compared the differences between the treatment groups with each outcome variable using a chi2 or a *t*-test, whether it was qualitative or quantitative, respectively. Statistical analyses were performed using STATA version 13.0. Treatments were divided into three categories: 1) oral progestin therapy only or combined with GnRH agonist, metformin or LNG-IUD, 2) HR followed progestin therapy, GnRH agonist, or LNG-IUD 3) LNG-IUD combined with GnRH or progestin therapy.

1.2. Results

318 studies were identified. After screening for titles and abstracts 85 were excludes, 9 were excluded because of duplication and 50 were excluded because they were reviews, meta-analyses or guides. Therefore, 174 were kept for fulltext reviewing reporting conservative treatment for endometrial cancer were included. Among these, 42

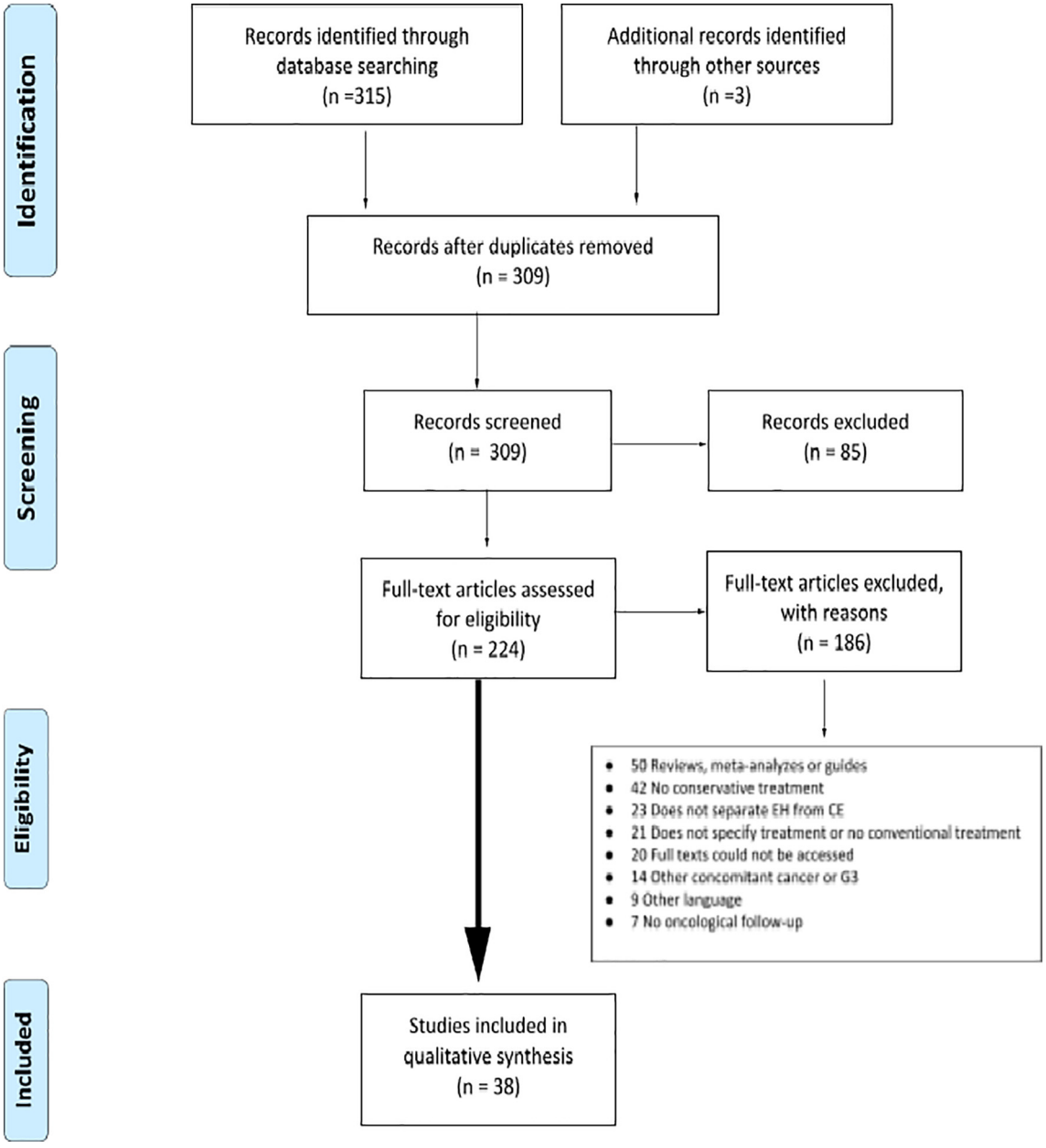

Fig. 1. Flow chart of study selection.

Table 1
Study quality was assessed utilizing a modified Newcastle–Ottawa study assessment scale by Gunderson.

Quality categories	High	Moderate	Low
Study design	Prospective	Prospective	Retrospective
Ascertainment of outcome	Follow-up for at least 5 years	Follow-up for >1 and < 5 years	Short follow-up of <1 year
n	2	10	26

they were not conservative treatment, 23 does not differentiate hyperplasia from cancer, 21 do not specified the treatment performed, 20 full texts could not be accessed, 14 other concomitant cancer or stage G3, 9 not English and 7 without cancer follow up. Finally 38 were determined eligible for this study (Fig. 1). A total of 38 studies reporting on 661 patients published between January 2010 through January 2020 were included. There were 13 prospective studies and 25 retrospective studies. Only two studies were considered of "high quality" as outlined by the study assessment criteria in Table 1 [19,20]. Ten of the prospective studies were considered of "medium quality" [14,15,21–28]. We found a prospective study with less than 12 months of follow-up [29], and with the others 25 retrospective studies were classified as "low quality" [11,12,30–52].

The mean age was 32.3 years (range 13–43). Gravidity was reported in 30 studies, and parity in 28, respectively. There were 25 studies that included only endometrial cancer and 13 studies that included endometrial cancer and atypical hyperplasia of those only included patients with endometrial cancer. The basic characteristics of the 38 studies are summarized in Table 2. Twenty-seven (71.05%) performed a pathological review.

Out of the 661 women, 79.4% had a complete response. The median follow-up was 54.9 months (range 3.4–412) for the progesterone group, 38.97 months (range 3–114) for the HR group and 23.11

Table 2
Characteristics and quality status of the studies included in the analysis.

	Year	N° Patients	Age (range/SD)	Histological diagnosis	Biopsy method	Follow Up in months (range/SD)	MRI	CR % (SD)	Time to CR in months (range/SD)	Relapse (n)	Primary treatment	Secondary treatment	Biopsy method	Pregnancies
Mao Y. et al.	2010	6	28 (26–31)	I	D&C or HSC	50.5(32–77)	yes	66,6	7.5 (3 to 9)	0	Progestagens	Progestagens		0
Perri T. et al.	2011	27	33.4 (24–43)	Well differentiated	D&C	57.4(7.8–412)	yes	88,8	5 (1–17)	15	Progestagens	Progestagens		14
Park H. et al.	2011	14	30 (21–38)	I	D&C	22.3(18–135)	yes	93	3	4	Progestagens	Progestagens		7
Dursun P. et al.	2012	43	31 (21–43)	I and II	D&C or HSC	49(5–156)	yes	85	5(2−12)	2	Progestagens	Progestagens		13
Fujiwara H. et al.	2012	59	31(21–42)	I	D&C	66(11–251)	yes	71	24.9(13–70)	22	Progestagens	Progestagens		17
Koskas M et al.	2012	8	34.3 (28–38)	I	D&C	39(14–86)	yes	62,5	6	2	Progestagens	Progestagens		2
Shan B. et al.	2013	14	30 (18–38)	Well differentiated	HSC	34.7(15–62)	yes	78,5	6	3	Progestagens	Progestagens		2
Jafari Shobeiri M. J. et al.	2013	8	30(24–35)	Well differentiated	D&C	34.5(11–72)	yes	87,5	6.5(3–9)	3	Progestagens	Progestagens		3
Park J.Y: et al	2013	148	31.3 (21–40)	I	D&C or HSC	66 (14–194)	yes	77,7	4.4(2–13.75)	35	Progestagens	Progestagens		44
Ohyagi-Hara C. et al.	2015	16	34.2(22–43)	I	D&C	39.2(3.4–153.8)	yes	68,8	3	1	Progestagens	Progestagens		1
Tamauchi S. et al.	2017	9	34(19–45)	I	D&C	52(16–128)	yes	88,8	10 (6.5–13)	7	Progestagens	Progestagens		3
Yang H.C.	2019	6	33.6(30–36)	I	HSC	32(4–49)	yes	100	7.5(6–9)	0	Progestagens	Progestagens		1
Uda H.	2019	1	14	I	D&C	11	yes	100	2	0	Progestagens	Progestagens		0
Tanmahasamut P. et al.	2010	1	24	Well differentiated	HSC	24	yes	100	9	0	Progestagens	LNG-IUD		0
Kim M. K. et al.	2011	5	38.4 (33–41)	I	D&C	10,2(6–16)	yes	80	12	0	Progestagens	LNG-IUD		0
Kim S. M. et al.	2016	1	13	II	not specified	9	yes	100	6	0	Progestagens	LNG-IUD		0
Hwang J.Y. et al.	2017	5	30.4(25–39)	II	D&C	44.4(12–71)	yes	60	11(9–19)	1	Progestagens	LNG-IUD		1
Chen M. et al.	2016	37	32(21–41)	I	D&C or HSC	54(4–148)	yes	72,9	6(3–24)	8	Progestagens	GnRH Agonist or LNG-IUD or Progestagens		8
Arendas K. et al.	2015	2	25 and 35	I	not specified	48 and 20	yes	100	3	1	Progestagens	HR		1
Zhou R. et al.	2015	19	30.4(20–40)	I	D&C or HSC	32.5(10–92)	yes	78,9	3	0	Progestagens	Metformin		4
Laurelli G. et al.	2011	14	38 (26–40)	Well differentiated	HSC	40(13–79)	yes	100	12	1	HR	LNG-IUD or Progestagens		1
Marton I. et al.	2012	2	30 and 39	I	HSC	20 and 16	not specified	100	3	0	HR	LNG-IUD or Progestagens		2
De Marzi P. et al.	2015	3	36.58 (23–43)	I	HSC	25 (8–37)	yes	100	4	1	HR	LNG-IUD or Progestagens		1
Falcone FC. et al.	2017	28	36 (25–40)	I	HSC	92(6–172)	yes	89,3	6(3–9)	2	HR	LNG-IUD or Progestagens		13
Mazzon I. et al.	2010	6	33 (27–39)	I	HSC	50.5 (21–82)	yes	100	3	0	HR	Progestagens		4
Wang Q. et al.	2015	6	29.5(25–34)	Well differentiated	D&C or HSC	48,5	yes	100	3	0	HR	Progestagens		3
Yang B. et al	2019	40	31(23–42)	I	D&C or HSC	9(3–53)	yes	90	6.7(1–18)	4	HR	Progestagens		6
Laurelli G. et al.	2016	21	38 (26–40)	I	HSC	79.4(30–114)	yes	85,7	6	1	HR	LNG-IUD		12
Giampaolino P. et al.	2019	14	35.1(20–44)	I	HSC	24	yes	78,6	3	2	HR	LNG-IUD		0
Casadio P. et al	2018	3	32–37-38	I	HSC	56(48–60)	yes	100	3	0	HR	GnRH Agonist or		2

Minig L. et al.	2011	14	34 (22–40)	I	D&C	29(4–102)	yes	57,1	6	2	LNG-IUD	Progestagens GnRH Agonist	1
Nucera G. et al	2013	1	38	Well differentiated	HSC	36	yes	100	4	0	LNG-IUD	GnRH Agonist	1
Pronin S. M. et al.	2015	32	33(28–42)	I	HSC	17(1–45)	yes	63	6	0	LNG-IUD	GnRH Agonist	3
Newtson A. M. et al.	2017	1	25	II	D&C or HSC	9	yes	100	3	0	LNG-IUD	GnRH Agonist	0
Brown A.J. et al.	2012	1	18	II	HSC	13	yes	100	3	0	LNG-IUD	LNG-IUD	0
Roberti Maggiore U.L. et al.	2019	20	EC G1 33.4+/− 5.0 EC G2 34.5 +/− 3.3	I and II	HSC	EC G1 85.3 +/− 48.3 EC G2 115.5 +/− 2.6	yes	EC G1 13/16 (81.3) EC G2 3/4 (75.0)	EC G1 5.0 +/− 2.9 EC G2 4.0 +/− 0	EC G1 5/13 (38.5) EC G2 3/3 (100)	LNG-IUD	LNG-IUD	8
Kim M. K. et al.	2013	16	34.8 (29–40)	Well differentiated	D&C	31.1(16–50)	yes	87,5	9.7(3–35)	2	LNG-IUD	Progestagens	3
Kudesia R. et al.	2014	10	38.5 +/− 4.2	I	D&C or HSC	21.3±24.1	yes	70	12	0	LNG-IUD	Progestagens	2

Abbreviations: Progestagens (Megestrol Acetate min 160 mg/dia max 320 mg/dia Medroxyprogesterone min 100 mg/dia max 600 mg/dia and others) HR: Hysteroscopic Resection LNG-IUD: (Levonorgestrel Intrauterine device). D&C: dilatation and curettage; HSC: hysteroscopic biopsy or hysteroscopic resection.

months (range 1–115.5) for the LNG-IUD group. The HR group had more complete response with 90% vs. 77.7% and 71.3% of the progesterone group and LNG-IUD respectively ($p = 0.02$). Median time to complete response was 5 months (range 3–12) for the progesterone group, 5.6 months (range 3–12) for HR group and 7.2 months (range 3–12) for LNG-IUD group, these results are significant for HR ($p = 0.04$) (Fig. 2Fig.3). The women who relapsed after a complete response were 42 (29.17%) for the progesterone group, 7 (6.93%) for the HR group and 10 (27.03%) for the LNG-IUD group with a statistically significant $p < 0.05$.

The progression rates were 3.5%, 12% and 19.5% for the hysteroscopic resection, progesterone and LNG-IUD groups respectively ($p = 0.03$). An evaluation of publication bias was performed for the complete response outcome comparing LNG-IUD vs HR (the outcome that was significant in the survival analysis), finding that there is no publication bias given that the funnel plot shows that the studies are distributed similar around the result (Fig. 4).

A total of 168 hysterectomies were registered with percentages such as 32.8% of 429 progesterone group, 9.4% of 137 for hysteroscopy resection and 14.7% of 95 for the LNG-IUD group. Those differences were statistically significant $p = 0.0001$. The patients who relapsed included 32 (76.1%), 6 (85.71%) and 10 (100%) for the progesterone, HR and LNG-IUD groups, were hysterectomized respectively. The follow-up time of the 38 studies analyzed was 47.92 (range, 1–412). It was 54.9 (range 3.4–412) months for the progesterone group, 38.97 (range 3–172) months for the HR group and 23.1 (range 1–115.5) months for the LNG-IUD group.

Out of the 429 patients who received primary treatment with progestogens, 121 pregnancies and 81 births were found. Out of 137 with primary treatment for HR, 44 became pregnant with 35 deliveries. Of the primary LNG-IUD treatment of 95 patients, 18 became pregnant with 11 deliveries. Patients who underwent HR had higher pregnancy rates compared to medical treatment or LNG-IUD, 34.5%, 27.6% and 18.4%, respectively ($p = 0.002$). Data on spontaneous versus assisted-pregnancies was not consistently reported, and therefore, the percentage of pregnancies resulting from assisted reproductive technologies could not be calculated.

2. Discussion

This review, which included 38 studies and 661 patients to compare oncologic and reproductive outcomes of fertility-sparing treatments in patients with grade 1 or 2 endometrial cancer, showed a complete response rate of 79.4% overall, and these results are similar to a previous meta-analysis report [52] but when we look at patients who underwent HR followed by progestagens the complete response rate was 90%.

The most commonly reported approach in the conservative management of patients with endometrial cancer is the use of progestational agents. Progestin therapy has an impact on the endometrial cells as early as 10 weeks after initiation of treatment, but most recognize the need for a minimum of 3 months of treatment before assessing for a response with endometrial hyperplasia and even longer for endometrial cancer [30].

The majority of patients reported in the literature have been treated with either medroxyprogesterone acetate or megestrol acetate with optimal dosage and duration of treatment. Because there is no consensus on the optimal dosage and duration of treatment in the different studies [54].

Current recommendations are MPA at a dose of 400–600 mg/day or MA at a dose of 160–320 mg/day for a minimum of 6 months, with a follow-up assessment of treatment response using D&C and imaging [7,55].

MA has been linked to higher remission probabilities compared to MPA and other hormonal treatments [56], which may be due to the relatively higher bioavailability of MA compared to MPA following oral administration [57].

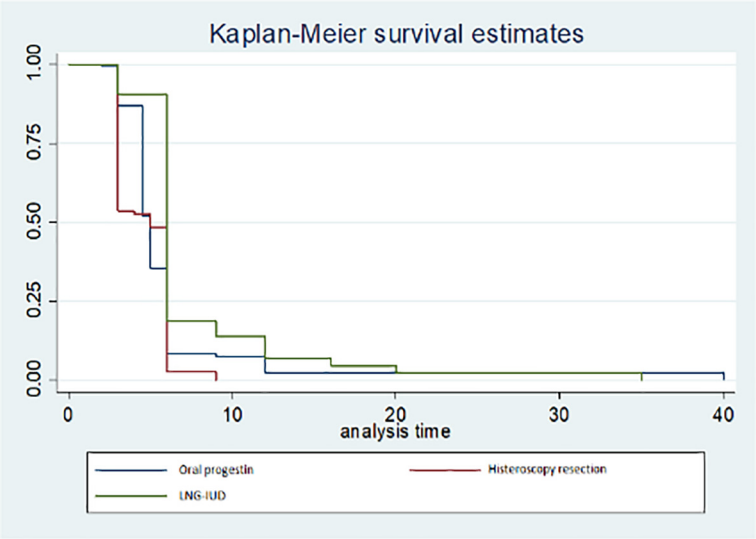

Fig. 2. Kaplan-Meier of complete response in different groups.

Ramirez et al. [58] published one of the initial comprehensive reviews in 2004. In this article, the authors gathered data published from 1966 to 2003, with a total of 81 patients who were treated with hormonal therapy. A total of 76% of patients responded to treatment, 24% recurred. The median response time was 12 weeks (range, 4–60 weeks), median time to recurrencewas 19 months (range, 6–44). These results are similar to our group of patients treated with progesterone.

The complete response rates in endometrial cancer treated with LNG-IUD are highly variable. In our review, a CR rate from 57.1% to 100% (15,27,28,48-52) was observed, with a total CR of 71.3%. Pal N et al [59], is the largest series published on patients who only underwent treatment with LNG-IUD, obtained a CR of 67% for G1 and 75% for G2, it is comparable with our results. We did not include this article in our review because it is a conservative but not fertility-sparing treatment. [60] A prospectiveobservation study of LNG-IUD for one year plus a GnRH analogue for 6 months in patients aged <40 years with stage 1A EC, showed results comparable to studies using MPA and MA, with a complete remission rate of 57% and a recurrence rate of 25% [15].

The LNG-IUD circumvents the issues with non-compliance patients that accompany oral medication, as well as the possible side-effects associated with high-dose oral progestins. A recent meta-analysis of 5 randomized controlled trials comparing the LNG-IUD to oral cyclic MPA treatment, found that although regression rates for both were similar overall, regression rates were higher for non-atypical endometrial hyperplasia and mixed (atypical and non-atypical) endometrial hyperplasia therapy among non-obese women [61].

A recent phase II trial by Westin et al. using Levonorgestrel Intrauterine Device (52 mg levonorgestrel, Mirena®) showed 66.7% response rates for patients with grade 1 endometrial cancer, 9.5% recurrence for atypical hyperplasia and endometrial cancer and no differences between responders and non-responders in age (44.5 vs 53.4y, $p = 0.10$) or BMI (43.4 vs 51.3, $p = 0.16$) [16].

Gunderson et al. [17] demonstrated complete response in a review of 304 women (77.7%) treated with progestogens. Median time to complete response was 6 months (range 1–18). A total of 208 women (53.2%) demonstrated a complete response with no evidence of recurrence. Ninety-six women (24.6%) exhibited an initial response but eventually developed recurrence, similar to our data.

Hysteroscopy as part of treatment is under discussion; while others take its use as limiting others find it challenging [62].

Leitao et al. [63] compared grade 1 tumors diagnosed preoperatively with dilatation and curettage (D&C) or pipelle biopsy and found that significantly fewer tumors diagnosed by D&C were upgraded in the final hysterectomy specimen, than those diagnosed by pipelle biopsy (8.7% vs. 17.4%; $P = 0.007$).

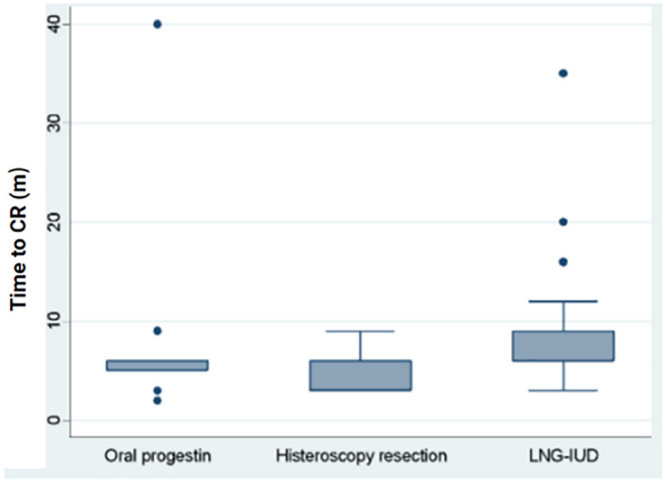

Fig. 3. Box plot of time to complete response in different group.

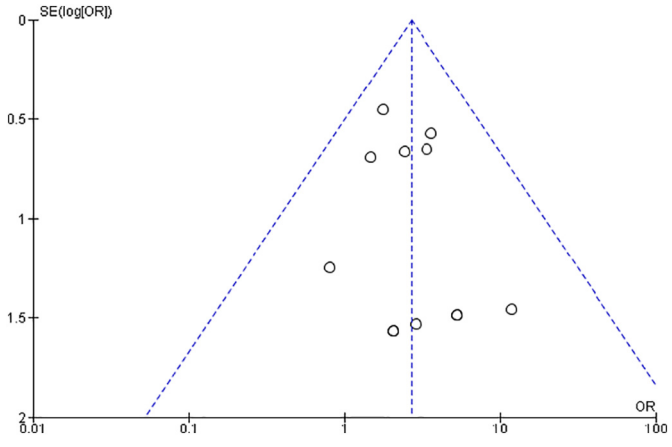

Fig. 4. Funnel plot assessment of publication bias for the complete response outcome comparing LNG- IUD vs Hysteroscopic resection.

A recent review by Visser et al. [64] showed that hysteroscopic biopsy as preoperative endometrial sampling method has higher consensus, with the final diagnosis. This could explain better outcomes in patients who underwent hysteroscopy resection. In fact, with a better diagnosis, there is less change in downgrading or upgrading the endometrial samples. This leads to a suitable selection, a more adapted treatment for the patient, and a better outcome overall.

Many claims that it allows for more selective removal of the primary disease site plus adjacent margins and myometrium and allows for a more accurate assessment of tumor characteristics through appropriate biopsy sampling. The elimination of much of the hyperplasia followed by the action of progestagens or LNG-IUD, would allow a synergistic action and thus observe better response in less time. Studies reporting results related to the use of hysteroscopy in conservative treatment are limited to case studies and case series.

Alonso et al. [65] reviewed studies published between 1975 and 2014 of EC patients aged <40 years treated with initial hysteroscopic resection followed by hormone therapy for fertility-sparing and found that the complete response rate for patients with stage 1A, grade 1 EC was 88.9%, similar to our findings.

The published literature shows that fertility results in patients with conservatively managed endometrial pathology are promising with pregnancy rates ranging from 25% to 100% according to different techniques [17,53,].

Removing a layer of endometrium may be detrimental to future fertility development; Falcone et al. [19] evaluated the impact of the hysteroscopy resection of the tumor, adjacent endometrium and myometrium underlaying the tumor. Their results were promising, with a remission rate of 96.3% and a live birth rate of 86.6%. However, the sample size was too small to make any formal conclusions about the impact of operative hysteroscopy on fertility.

The current literature indicates that assisted reproduction after a complete response are not associated with an increased risk of recurrence [55]; furthermore, Park et al. [66] reported that disease-free survival was greater among patients who had achieved at least one pregnancy compared with those who had not [54].

To our knowledge this is one of the largest reviews of the literature that includes only patients with endometrial cancer, limitations of this study include the retrospective nature of the review and thus inherent reporting and observational biases, lack of long term follow-up data for most studies, and inconsistent reporting of reproductive outcomes.

In conclusion hysteroscopy resection followed progestogens agent was associated to a better complete response, high pregnancy rates and lower rates of hysterectomies.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Author contribution

Lucchini S.M: Methodology, Investigation, Writing - Original Draft, Supervision, Project administration. Esteban A: Investigation, Writing - Review & Editing, Supervision, Funding acquisition. Nigra M.A: Resources, Data Curation. Palacios A.T: Methodology, Resources, Visualization. Alzate-Granados J.P: Software, Formal analysis. Borla H·F: Resources, Data Curation, Writing - Original Draft, Project administration.

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