**Human Reproduction Update, Vol.28, No.2, pp. 282–295, 2022**
Advance Access Publication on December 22, 2021 https://doi.org/10.1093/humupd/dmab041

human reproduction update

# Chances of pregnancy and live birth among women undergoing conservative management of early-stage endometrial cancer: a systematic review and meta-analysis

**Erica Herrera Cappelletti[1,2], Jonas Humann[2], Rafael Torrejón[2], and Pietro Gambadauro [1,2,3,4,*]**

[1]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden [2]Area of Obstetrics and Gynaecology, University of Cádiz, Cádiz, Spain [3]Department of Learning, Informatics, Management and Ethics (LIME), Karolinska Institutet, Stockholm, Sweden [4]Res Medica Sweden, Uppsala, Sweden

*Correspondence address. E-mail: gambadauro@gmail.com; pietro.gambadauro@ki.se; pietro.gambadauro@kbh.uu.se
https://orcid.org/0000-0003-1568-4575

*Submitted on July 20, 2021; resubmitted on November 08, 2021; editorial decision on November 17, 2021*

## TABLE OF CONTENTS

- Introduction
- Methods
  - Search strategy
  - Study selection
  - Data management
  - Synthesis of results
  - Study registration
- Results
  - Selection and characteristics of the studies
  - Quantitative synthesis
- Discussion
  - Main findings
  - Strengths and limitations
  - Interpretation
  - Implications
  - Conclusions

**BACKGROUND:** Endometrial cancer is common and usually occurs after menopause, but the number of women diagnosed during reproductive age is increasing. The standard treatment including hysterectomy is effective but causes absolute uterine factor infertility. In order to avoid or postpone surgery, conservative management of endometrial cancer (CMEC) has been proposed for younger women who want to retain their fertility.

**OBJECTIVE AND RATIONALE:** The main objective of this study was to estimate the chances of pregnancy and live birth for women with early-stage endometrial cancer (EEC) who are managed conservatively for fertility preservation.

**SEARCH METHODS:** The PRISMA recommendations for systematic reviews and meta-analyses were followed. Structured searches were performed in PubMed, Embase and the Cochrane Library, from inception until 13 June 2021. Inclusion was based on the following criteria: group or subgroup of women with Clinical Stage IA, well-differentiated, endometrioid endometrial cancer (from now on, EEC); CMEC for fertility preservation; and reported frequencies of women achieving pregnancy and/or live birth after CMEC. The following exclusion criteria applied: impossibility to isolate/extract outcome data of interest; second-line CMEC for persistent/recurrent disease; CMEC in the presence of synchronous tumours; case reports; non-original or duplicated data; and articles not in English. Qualitative synthesis was performed by means of tabulation and narrative review of the study characteristics. Study quality was assessed with an *ad hoc* instrument and several moderator and sensitivity analyses were performed.

**OUTCOMES:** Out of 1275 unique records, 133 were assessed in full-text and 46 studies were included in the review. Data from 861 women with EEC undergoing CMEC were available. Progestin-based treatment was reported in all but three studies (93.5%; 836 women). Complete response to treatment was achieved in 79.7% of women, with 35.3% of them having a disease recurrence during follow-up. Of 286 pregnancies obtained after CMEC; 69.4% led to live birth (9% of them multiple births) and 66.7% were achieved through fertility treatment. Based on random-effects meta-analyses, women treated with progestin-based CMEC have a 26.7% chance of achieving pregnancy (95% CI 21.3–32.3; $I^2 = 53.7\%$; 42 studies, 826 women) and a 20.5% chance to achieve a live birth (95% CI 15.7–25.8; $I^2 = 40.2\%$; 39 studies, 650 women). Sample size, average age, publication year, study design and quality score were not associated with the outcomes of progestin-based CMEC in moderator analyses with meta-regression. However, mean follow-up length (in months) was positively associated with the chances of pregnancy (regression coefficient [*B*] = 0.003; 95% CI 0.001–0.005; $P = 0.006$) and live birth ($B = 0.005$; 95% CI 0.003–0.007; $P < 0.001$). In sensitivity analyses, the highest chances of live birth were estimated in subsets of studies including only women of age 35 or younger (30.7%), the combination of progestins with hysteroscopic resection (30.7%), or at least 3 years of follow-up (42.4%).

**WIDER IMPLICATIONS:** Progestin-based CMEC is viable for women with well-differentiated, Clinical Stage 1A, endometrioid endometrial cancer who want to preserve their fertility, but there is room for improvement as only one-fifth of them are estimated to achieve live birth according to this meta-analysis. Further investigations on prognosis-driven selection, hysteroscopic resection and long-term surveillance are arguably needed to improve the reproductive outcomes of CMEC.

**Key words:** absolute uterine factor infertility / conservative management / endometrial cancer / fertility preservation / hysteroscopy / progestins / reproductive medicine / reproductive outcome

# Introduction

Endometrial cancer is one of the most frequent malignancies in women and its incidence has been increasing during the last decades (Morice *et al.*, 2016; Lortet-Tieulent *et al.*, 2018; Constantine *et al.*, 2019). Most women diagnosed with endometrial cancer are postmenopausal, and the standard management requires hysterectomy with bilateral salpingo-oophorectomy (Morice *et al.*, 2016; Hamilton *et al.*, 2021a). This surgical approach is effective but can be particularly problematic for younger women who wish to retain their fertility (Gambadauro and Gudmundsson, 2017). Although these women are a minority of the total cases (~14% of them being premenopausal and 5% younger than 40 years), their number is likely to grow because of the increasing incidence of endometrial cancer, the delay in childbearing across societies and the inverse relationship between parity and endometrial cancer risk (Rodolakis *et al.*, 2015; Morice *et al.*, 2016; Raglan *et al.*, 2019; Hamilton *et al.*, 2021b).

An alternative conservative management of endometrial cancer (CMEC) has therefore been proposed and is deemed appropriate for younger women with well-differentiated, early stage (Clinical Stage IA, ideally without myometrial involvement), endometrioid endometrial cancer (Rodolakis *et al.*, 2015; Hamilton *et al.*, 2021b). This conservative strategy aims at avoiding or postponing the standard treatment, most commonly by means of a course of oral or intrauterine progestins (Rodolakis *et al.*, 2015; Hamilton *et al.*, 2021b). Pregnancy may be attempted if and once a response is achieved, whereas hysterectomy is recommended as soon as childbearing is complete or in case of treatment failures (Rodolakis *et al.*, 2015; Hamilton *et al.*, 2021b).

The choice between the gold-standard surgical treatment and the alternative CMEC in order to preserve fertility can be challenging. The burden of absolute uterine factor infertility among cancer survivors deserves to be addressed (Bower and Quinn, 2012). However, although most women respond to CMEC, departing from the standard treatment may worsen the oncological outcomes (Gallos *et al.*, 2012; Gunderson *et al.*, 2012). Besides, the evidence base regarding the reproductive outcomes after CMEC largely consists of small-sample cohorts or case series whose reported pregnancy and live birth rates may be misleading and cannot be uncritically generalized (Ruiz *et al.*, 2017; Wei *et al.*, 2017; Gambadauro, 2020). In addition, recent population-based data indicate that fewer than expected live births are being reported among women who undergo CMEC in a real-life setting (Harrison *et al.*, 2019).

The aim of this study was to evaluate the reproductive outcomes of CMEC through a systematic review and meta-analysis of published data. The main objective was to estimate the chances of pregnancy and live birth for women with early-stage endometrial cancer (EEC) who are treated conservatively for fertility preservation. A secondary objective was to describe oncological outcomes, mode of conception and pregnancy outcomes after CMEC.

# Methods

## Search strategy

In the present study, the recommendations of the PRISMA statement for systematic reviews and meta-analyses (Moher *et al.*, 2009) were

followed. Structured searches were performed in PubMed, Embase and the Cochrane Library, with no start date and until 13 June 2021. The search strategy included combinations of free terms, with variations and controlled vocabulary (e.g. MeSH terms/descriptors), based on the following themes: endometrial neoplasms, endometrial cancer, endometrial hyperplasia, fertility preservation, fertility sparing and conservative treatment (Supplementary Data File S1).

## Study selection

The search results were saved into a reference manager (Mendeley Desktop, version 1.19.8). After duplicates removal, the citations were screened based on their title and abstract. Selected items were evaluated for eligibility in full-text. Inclusion was based on the following criteria: the presence of a group or subgroup of women with Clinical Stage IA, well-differentiated (i.e. Grade 1 or G1), endometrioid endometrial cancer (from now on, EEC); CMEC for fertility preservation; and reported frequencies of women achieving pregnancy and/or live birth after CMEC. The following exclusion criteria applied: impossibility to isolate/extract outcome data of interest; second-line CMEC for persistent/recurrent disease; CMEC in the presence of synchronous tumours; case reports; non-original or duplicated data; and articles not in English.

## Data management

A data extraction form was developed in order to systematically extract the following data: number of women with EEC undergoing CMEC; number of women achieving pregnancy and live birth; type of CMEC; average age; follow-up length; oncological outcomes (i.e. complete response to treatment, recurrence, disease-related deaths); and reproductive outcomes (i.e. pregnancies, live births, mode of conception). Study characteristics such as the year of publication, the country of origin and the design were also recorded. The data were eventually saved in a digital spreadsheet.

## Synthesis of results

The studies were screened, selected and reviewed independently by two researchers (E.H.C., J.H. or P.G.). Disagreements were solved through discussion or a third researcher's judgement (P.G. or R.T.). Qualitative synthesis was performed by means of tabulation and narrative review of the study characteristics. The quality of the studies was assessed with an *ad hoc* tool for Single-Arm Study Quality Assessment (Supplementary Data File S2), which was developed from items of the Newcastle-Ottawa Scale (Wells *et al.*, 2021) and the Methodological Index for Non-Randomized Studies (Slim *et al.*, 2003). The studies were categorized as cohort or case series based on the criteria proposed by Schünemann *et al.* (2008; Supplementary Data File S2).

For the quantitative synthesis of primary outcomes, the chances of pregnancy and live birth were estimated by means of pooling data from individual studies in meta-analysis of proportions, where the numerator was the number of women with the outcome of interest (i.e. pregnancy or live birth) and the denominator was the number of women with EEC exposed to the intervention (i.e. CMEC). The secondary outcomes were synthesized descriptively, through pooling of individual study data on complete responses to treatment, disease recurrence, disease-related deaths, mode of conception (i.e. spontaneous or via fertility treatment) and pregnancy outcome (i.e. live birth, pregnancy loss, multiple birth).

Random-effects meta-analyses were carried out in R with OpenMeta[analyst] for MacOS (School of Public Health, Brown University, USA; Wallace *et al.*, 2012; Center for Evidence Synthesis in Health (CESH), 2021), using the Freeman–Tukey transformation (Murad *et al.*, 2018). Proportions were estimated together with 95% CI. The $I^2$ statistic was used to study heterogeneity. The analyses were performed in the main subset of studies including a progestin-based treatment, which is the dominant option for CMEC as well as in the overall study sample. Several moderator and sensitivity analyses were conducted in the main subset of studies. Moderator analyses with meta-regression were performed in order to study potential effect modifiers, such as sample size, average age, average follow-up length, publication year, study design and quality score. Sensitivity analyses were performed with the leave-one-out strategy as well as by means of repeating the meta-analyses in subsets of studies defined by criteria related to age ($\leq$40, $\leq$38 and $\leq$35), disease stage (EEC without myometrial invasion), type of CMEC (progestins combined with hysteroscopic resection), follow-up time ($\geq$12, $\geq$24 and $\geq$36 months), sample size ($\geq$10 women) and quality score ($\geq$7).

## Study registration

A protocol was prospectively registered in PROSPERO (Centre for Reviews and Dissemination, University of York, UK; http://www.crd.york.ac.uk/PROSPERO/; National Institute for Health Research (NIHR), 2021) as CRD42020086867.

# Results

## Selection and characteristics of the studies

The search queries returned 1649 records (383 of them duplicates), which were screened based on title and abstract (Fig. 1). Nine additional studies were identified through handsearching. Out of 133 items assessed in full-text, 46 articles published between 2001 and 2021 were selected for inclusion in the systematic review and provided data for meta-analysis (Table I). Relevant proportions of the articles were, respectively, published since 2010 (82.6%) and since 2015 (45.7%). Most studies proceeded from Asia (69.6%), followed by Europe (23.9%), North America (4.3%) and Oceania (2.2%).

In total, 861 women undergoing CMEC were identified for review: a mean of 18.7 women per study (median 10.5; range 3–177). These women had been diagnosed with EEC, as previously defined, and myometrial invasion was systematically ruled out in 84.8% of studies. The mean age across the studies ranged from 25.1 to 38.5; 4 studies (8.7%) included women aged 45 or older, whereas 32 (69.6%) solely selected women aged 40 or younger. Information regarding the type of CMEC reported in each study is presented in Table I. The CMEC strategy was based on progestins in 43 of the 46 studies (93.5%; 836 women). In 37 studies, daily doses of medroxyprogesterone acetate (MPA; up to 800 mg) or megestrol acetate (MA; up to 480 mg) were administered orally, most commonly for at least 3–6 months. Alternative or complementary routes of progestin administration were intrauterine (11 studies) and intramuscular (3 studies). GnRH agonists were used in combination with progestins in five studies. In 12 studies, progestin-based treatment was preceded by hysteroscopic resection. Only three studies (6.5%) reported treatments alternative to

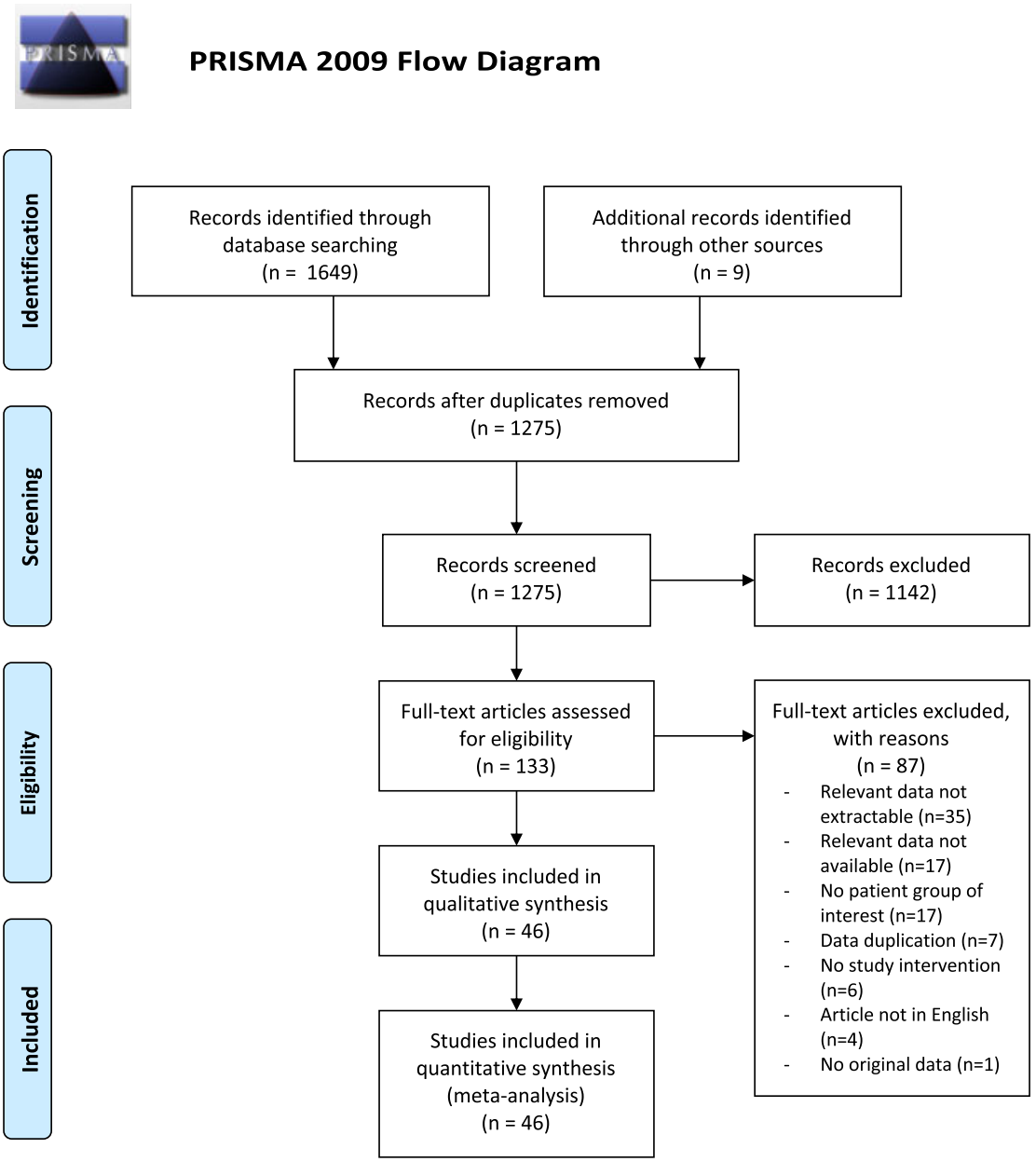


**Figure 1. Study flowchart.** Taken from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. https://doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

progestins, consisting of intravenous photosensitizer and photodynamic therapy (11 patients; Choi *et al.*, 2013), the combination of GnRH agonists and hysteroscopic resection (8 patients; Tock *et al.*, 2018), and the combination of GnRH agonists and aromatase inhibitors (6 patients; Zhang *et al.*, 2019). The mean follow-up length across the studies ranged from 16.7 to 196.5 months.

The studies had either a cohort (47.8%) or case series (52.2%) design, most of them being retrospective (67.4%). Quality assessment returned a mean quality score of 6.6 out of 10 possible points (median 6.5; range 3–9). Exposure ascertainment was satisfactory in all studies; loss to follow-up was addressed in 70% of them and the main outcome live birth was available in 42 of them (91.3%). The main limitations concerned sample size (prospective calculation, 0%) and case selection (representativeness, 60.9%; report of excluded patients, 34.8%; Supplementary Table SI).

## Quantitative synthesis

### *Primary outcomes*

Based on a meta-analysis of 42 studies (826 women), the chance of pregnancy for women treated with progestin-based CMEC for fertility

**Table I General characteristics of the included studies.**

| Reference | Year | Country | Study design | Subjects with EEC | Mean age (range) | Type of treatment | Subjects with complete response (%) | Mean follow-up in months (range) | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Andress et al. | 2021 | Germany | Cohort study | 10 | 34.3 (30.2–47.9) | Progestins (O) | 5 (50%) | 16.7 (4–40) | 6 |
| Atallah et al. | 2021 | Lebanon | Case series | 6 | NK (NK–40) | Progestins (O) + Hysteroscopic resection + GnRH agonists | 6 (100%) | NK (12–NK) | 4 |
| Ayhan et al. | 2020 | Turkey | Cohort study | 30 | 32 (20–45) | Progestins (O and/or IU) + Hysteroscopic resection | 22 (73.3%) | 55.5 (6–133) | 7 |
| Cade et al. | 2013 | Australia | Cohort study | 10 | 32 (23–42) | Progestins (O and/or IU) | 10 (100%) | 89.2 (62–142) | 8 |
| Casadio et al. | 2018 | Italy | Case series | 3 | 35.7 (32–38) | Progestins (O) + Hysteroscopic resection + GnRH agonists | 3 (100%) | 60 (60) | 4 |
| Casadio et al. | 2020 | Italy | Case series | 36 | 33.1 (NK–45) | Progestins (O) + Hysteroscopic resection | 35 (97.2%) | 30 (24–60) | 6 |
| Chen et al. | 2016 | China | Cohort study | 37 | 32 (21–41) | Progestins (O) | 27 (73%) | 54 (4–148) | 9 |
| Choi et al. | 2013 | Korea | Case series | 11 | 31.5 (28–34) | Photodynamic therapy + IV photosensitizer | 7 (63.6%) | 82.7 (37–115) | 8 |
| Duska et al. | 2001 | USA | Cohort study | 12 | 30.8 (24–40) | Progestins | 10 (83.3%) | NK | 6 |
| Falcone et al. | 2017 | Italy | Cohort study | 27 | 36 (25–40) | Progestins (O or IU) + Hysteroscopic resection | 26 (96.3%) | 96 (6–172) | 9 |
| Giampaolino et al. | 2019 | Italy | Case series | 14 | 35.1 (NK–44) | Progestins (IU) + Hysteroscopic resection | 11 (78.6%) | NK (12–24) | 6 |
| Gungor et al. | 2016 | Turkey | Case series | 6 | 34.3 (30–40) | Progestins (O or O+IU) | 5 (83.3%) | 45 (3–75) | 6 |
| Imai et al. | 2001 | Japan | Case series | 5 | NK (NK–38) | Progestins (O) | NK | 67.2 (10–146) | 6 |
| Kaku et al. | 2001 | Japan | Case series | 10 | 30.7 (21–40) | Progestins (O) | 7 (70%) | 33.6 (13–90) | 7 |
| Kataoka et al. | 2014 | Japan | Case series | 7 | 32.6 (21–38) | Progestins (O) | 4 (57.1%) | NK | 5 |
| Kim et al. | 2013 | Korea | Case series | 16 | 34.8 (29–40) | Progestins (O+IU) | 14 (87.5%) | 31.1 (16–50) | 6 |
| Koskas et al. | 2012 | France | Cohort study | 8 | 34.4 (28–38) | Progestins (O) | 5 (62.5%) | 50.3 (17–86) | 8 |
| Kudesia et al. | 2014 | USA | Cohort study | 10 | 38.5 (NK–44) | Progestins (O and/or IU) | 7 (70%) | 21.3 (NK) | 7 |
| Maggiore et al. | 2019 | Italy | Case series | 16 | 33.4 (NK) | Progestins (IU) | 13 (81.3%) | 85.3 (NK) | 6 |
| Mao et al. | 2010 | China | Case series | 6 | 28 (26–31) | Progestins (O) | 4 (66.7%) | 50.5 (32–77) | 6 |
| Mazzon et al. | 2020 | Italy | Case series | 6 | 32.5 (27–39) | Progestins (O) + Hysteroscopic resection | 6 (100%) | 196.5 (164–228) | 5 |
| Minaguchi et al. | 2007 | Japan | Cohort study | 19 | 30.5 (19–37) | Progestins (O) | 15 (78.9%) | 45.1 (2–109) | 5 |
| Minig et al. | 2011 | Italy | Cohort study | 14 | 34 (22–40) | Progestins (IU) + GnRH agonists | 8 (57.1%) | 29 (4–102) | 9 |
| Niwa et al. | 2005 | Japan | Case series | 10 | 30.4 (24–34) | Progestins (O) | 10 (100%) | 52.2 (24–138) | 8 |
| Ohyagi-Hara et al. | 2015 | Japan | Case series | 16 | NK (NK) | Progestins (O) | 11 (68.8%) | NK | 6 |
| Ota et al. | 2005 | Japan | Case series | 12 | 30.9 (22–40) | Progestins (O) | 5 (41.7%) | 52.7 (13–154) | 6 |
| Park et al. | 2013 | Korea | Cohort study | 177 | NK (NK–39) | Progestins (O) | 141 (79.7%) | NK | 7 |
| Parlakgumus et al. | 2014 | Turkey | Case series | 3 | 34.3 (28–38) | Progestins (O) | 3 (100%) | NK | 4 |
| Pashov et al. | 2012 | Russia | Case series | 11 | 30.2 (26–36) | Progestins (IU) + GnRH agonists | 11 (100%) | 44.4 (24–72) | 6 |

Continued

**Table I Continued**

| Reference | Year | Country | Study design | Subjects with EEC | Mean age (range) | Type of treatment | Subjects with complete response (%) | Mean follow-up in months (range) | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Perri *et al.* | 2011 | Israel | Cohort study | 25 | NK (NK) | Progestins (O or IM) | 22 (88%) | NK | 7 |
| Raffone *et al.* | 2021 | Italy | Cohort study | 6 | 35.5 (NK–44) | Progestins (IU) + Hysteroscopic resection | 2 (33.3%) | NK (12–NK) | 6 |
| Shan *et al.* | 2013 | China | Cohort study | 14 | 30.1 (18–39) | Progestins (O) | 11 (78.6%) | 34.7 (15–66) | 9 |
| Shirali *et al.* | 2012 | Iran | Cohort study | 16 | 33.1 (24–42) | Progestins (O) | 10 (62.5%) | NK (NK–125) | 7 |
| Shobeiri *et al.* | 2013 | Iran | Case series | 8 | 30 (24–35) | Progestins (O) | 7 (87.5%) | NK (NK–72) | 7 |
| Tamauchi *et al.* | 2018 | Japan | Cohort study | 9 | 34 (19–45) | Progestins (O) | 8 (88.9%) | 52 (16–128) | 6 |
| Tock *et al.* | 2018 | Belgium | Cohort study | 8 | 30.4 (18–38) | Hysteroscopic resection + GnRH agonists | 5 (62.5%) | 25.3 (5–72) | 8 |
| Ushijima *et al.* | 2007 | Japan | Cohort study | 28 | 31.7 (22–39) | Progestins (O) | 14 (50%) | 47.9 (25–73) | 9 |
| Wang *et al.* | 2014 | Taiwan | Cohort study | 37 | 32 (18–40) | Progestins (O) + Hysteroscopic resection | 30 (81.1%) | 78.6 (19.1–252.8) | 8 |
| Wang *et al.* | 2015 | China | Case series | 6 | 29.5 (25–34) | Progestins (O) + Hysteroscopic resection | 6 (100%) | 48.5 (26–91) | 7 |
| Wang *et al.* | 2017 | China | Case series | 11 | 27.3 (25–39) | Progestins (O or IM) + Hysteroscopic resection | 9 (81.8%) | 82.3 (15–152) | 8 |
| Yamagami *et al.* | 2018 | Japan | Cohort study | 97 | 35 (19–44) | Progestins (O) | 88 (90.7%) | 71.3 (4.5–208.7) | 3 |
| Yamazawa *et al.* | 2007 | Japan | Cohort study | 9 | 36 (28–40) | Progestins (O) | 7 (77.8%) | 38.9 (24–69) | 8 |
| Yang *et al.* | 2019 | Taiwan | Case series | 6 | 33.7 (30–36) | Progestins (O) + Hysteroscopic resection | 6 (100%) | 32 (4–49) | 5 |
| Yu *et al.* | 2009 | China | Case series | 8 | 25.1 (NK–35) | Progestins (O or IM) | 5 (62.5%) | 31.8 (5–90) | 8 |
| Zhang *et al.* | 2019 | China | Case series | 6 | 30.5 (NK–40) | GnRH agonists + aromatase inhibitors | 6 (100%) | 48 (15–84) | 7 |
| Zhou *et al.* | 2015 | China | Cohort study | 19 | 30.4 (20–40) | Progestins (O) | 15 (78.9%) | 32.5 (10–92) | 6 |

EEC, early-stage endometrial cancer; IM, intramuscular; IU, intrauterine; IV, intravenous; NK, not known; O, oral.

preservation was 26.7% (95% CI 21.3–32.3; $I^2 = 53.7\%$; Fig. 2). The chance of achieving a live birth after progestin-based CMEC was 20.5% (95% CI 15.7–25.8; $I^2 = 40.2\%$), based on a meta-analysis of 39 studies (650 women; Fig. 3). Similar overall estimates were obtained when excluding the three studies with non-progestin-based CMEC, namely 27.3% (95% CI 22.1–32.8; $I^2 = 52.0\%$) for pregnancy and 21.1% (95% CI 16.4–26.1; $I^2 = 37.0\%$) for live birth (Supplementary Figs S1 and S2).

In moderator analysis with meta-regression, no significant association was found between the reproductive outcomes of progestin-based CMEC and several study characteristics including sample size, average age, publication year, study design and quality score. On the contrary, mean follow-up length (in months) was positively associated with the estimated chance of pregnancy (regression coefficient [$B$] = 0.003; 95% CI 0.001–0.005; $P = 0.006$) and live birth ($B = 0.005$; 95% CI 0.003–0.007; $P < 0.001$; Supplementary Figs S3 and S4).

Sensitivity analyses with the leave-one-out strategy did not significantly affect the results. The largest albeit non-significant differences were 1.4 percentage-points in the chance of pregnancy (25.3%; 95% CI 20.3–30.6; $I^2$ 45.8%) when excluding Casadio *et al.* (2020) and 1.2 percentage-points in the chance of live birth (19.3%; 95% CI 14.7–24.3; $I^2$ 33.5%) when excluding Falcone *et al.* (2017).

Further sensitivity analyses revealed the stability of the results in subsets of studies with no myometrial invasion, larger sample size or higher quality score, with less than two percentage point differences from the main analyses and overlapping CIs (Table II). Larger differences from the main meta-analyses were observed when pooling subsets of studies including only women of age 35 or younger (low heterogeneity), combining progestin-based CMEC with hysteroscopic resection (moderate to substantial heterogeneity), or with at least 36 months of follow-up (low heterogeneity; Table II; Supplementary Figs S5, S6, S7).

### *Secondary outcomes*

Complete response to treatment was reported in 79.7% of 856 women (Table III) and ranged between 33.3% and 100% across 45

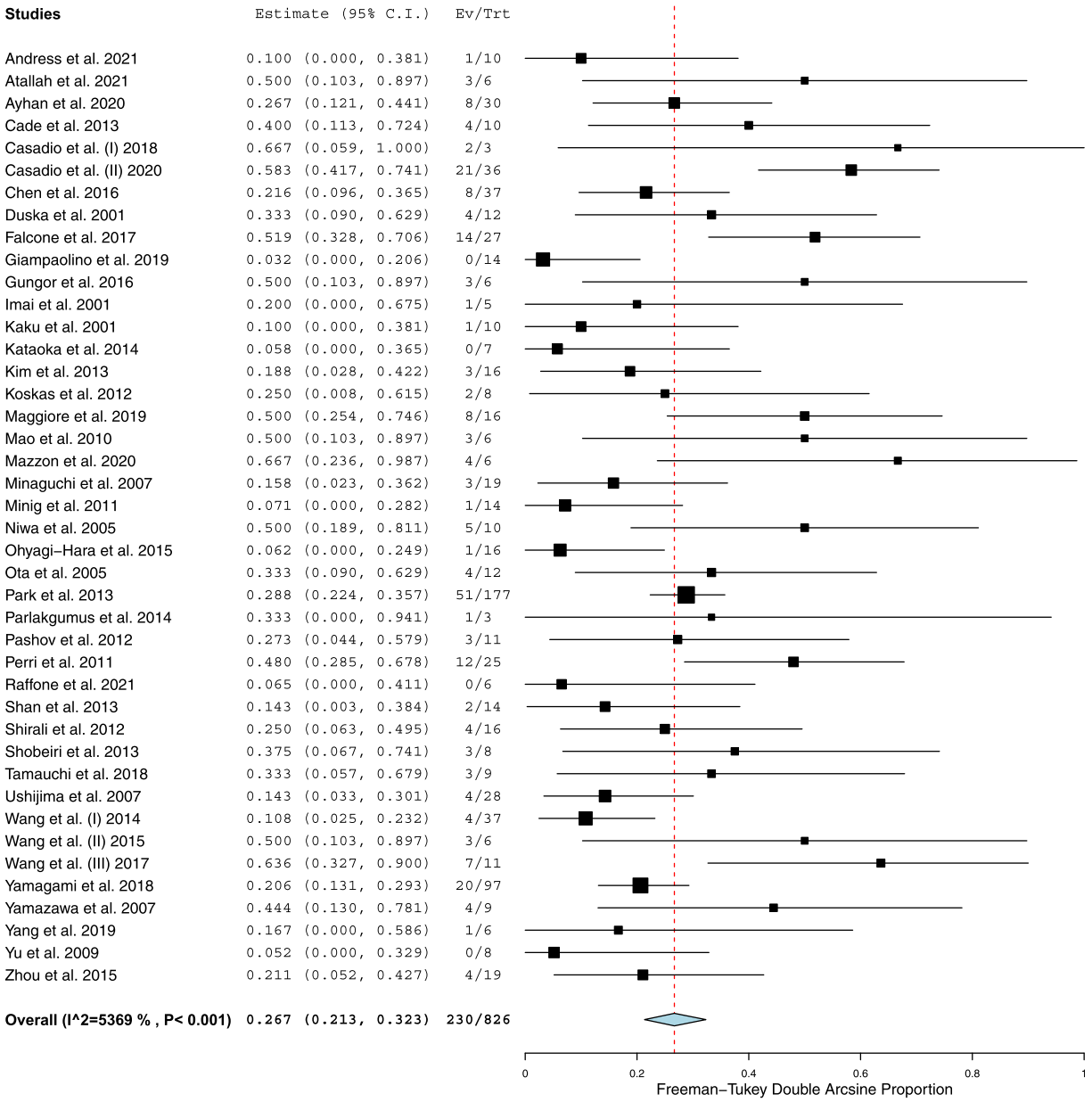


**Figure 2. Chances of pregnancy for women undergoing progestin-based conservative management of early-stage endometrial cancer.**

individual studies (data missing from Imai *et al.*, 2001). A similar complete response rate was observed when considering only studies with progestin-based CMEC (79.9%; 831 women, 42 studies). Disease recurrence was diagnosed in 35.3% of 665 women with previous complete response (Table III), ranging between 0% and 100% across 43 studies (incomplete data from Imai *et al.*, 2001; Shirali *et al.*, 2012; Kudesia *et al.*, 2014). Among all of the women included in the review, a single disease-related death occurring during follow-up was reported by Ota *et al.* (2005).

A total of 286 pregnancies after CMEC, reported from 44 studies, were reviewed, after the exclusion of two studies because of incomplete data (Kudesia *et al.*, 2014; Yamagami *et al.*, 2018). Regarding the mode of conception, 33.3% pregnancies were spontaneous, while 66.7% were obtained through fertility treatments (Table IV). The proportion of pregnancies leading to live birth was 69.4% and 9% of them resulted in multiple births (Table IV).

# Discussion

## Main findings

This study investigated the chances of pregnancy and live birth among women with EEC who undergo CMEC for fertility preservation,

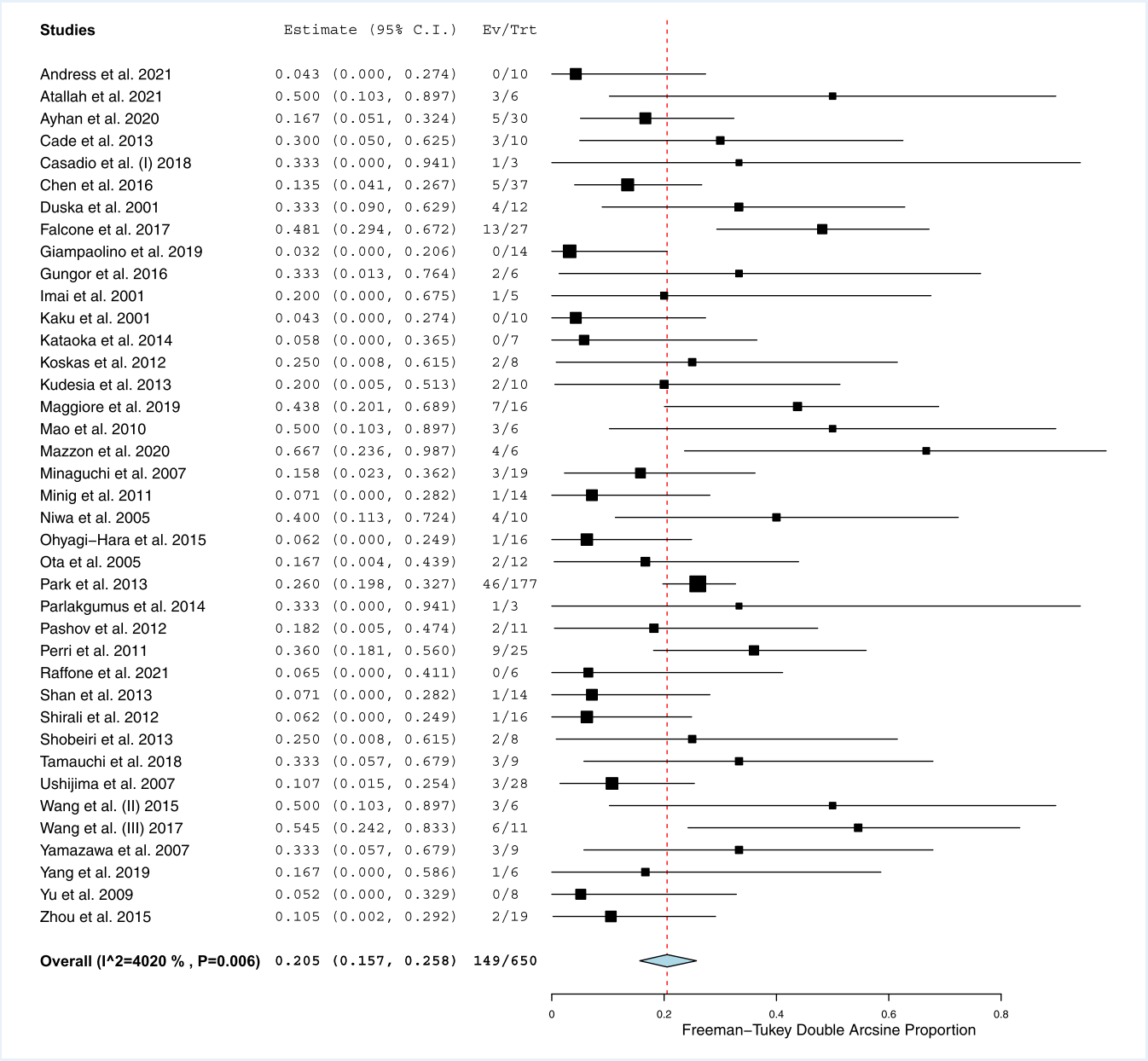


**Figure 3. Chances of live birth for women undergoing progestin-based conservative management of early-stage endometrial cancer.**

through meta-analysis of data proceeding from a total of 46 studies and 861 women. All but three studies reported progestin-based treatment (836 women). Overall, complete response to treatment was achieved in 79.7% of women, 35.3% of them having a disease recurrence during follow-up. Random-effects meta-analyses estimated that about one-quarter of women (26.7%) treated with progestin-based CMEC will achieve pregnancy and one-fifth of them (20.5%) will eventually have a live birth. Similar estimates were obtained when including the three studies with non-progestin-based CMEC. Sample size, average age, publication year, study design and quality score were not associated with the outcomes of progestin-based CMEC in moderator analyses with meta-regression. However, mean follow-up length was positively associated with estimated chances of pregnancy and live birth. In sensitivity analyses, the highest chances were estimated when pooling subsets of studies including only women of age 35 or younger (35.8% pregnancy; 30.7% live birth), the combination of progestin-based CMEC with hysteroscopic resection (34.0% pregnancy; 30.7% live birth) or at least 3 years of follow-up (51.4% pregnancy; 42.4% live birth). Among a total of 286 pregnancies reviewed, 69.4% led to live birth (9% of them multiple births) and two-thirds were achieved through fertility treatment.

## Strengths and limitations

Among the study's strengths are the comprehensive literature search and a systematic and reproducible review process. Many studies

**Table II Sensitivity analyses in subsets of studies on progestin-based conservative management of early-stage endometrial cancer.**

| Subset | Pregnancy | | | Live birth | | |
|---|---|---|---|---|---|---|
| | n women/studies | Estimate (95% CI) | $I^2$ | n women/studies | Estimate (95% CI) | $I^2$ |
| **Sample size ≥10** | 724/26 | 25.7% (19.7–32.1%) | 64.2% | 548/23 | 18.9% (13.4–24.9%) | 52.6% |
| **Maximum age** | | | | | | |
| 40 | 485/28 | 27.2% (20.4–34.3%) | 44.7% | 451/27 | 23% (16.8–29.7%) | 36.1% |
| 38 | 100/13 | 25.5% (15.9–36%) | 6.2% | 100/13 | 21.5% (12.8–31.3%) | 0% |
| 35 | 38/5 | 35.8% (16.8–56.9%) | 34.3% | 38/5 | 30.7% (13.7–50.3%) | 25.7% |
| **Hysteroscopic resection** | 182/11 | 34% (18.1–51.6%) | 77.2% | 115/10 | 30.7% (15.6–47.8%) | 61.8% |
| **No myometrial invasion** | 735/35 | 25.5% (20.1–31.3%) | 50.6% | 579/32 | 22.3% (16.8–28.2%) | 44.2% |
| **Minimum follow-up** | | | | | | |
| 12 months | 461/23 | 30.9% (22.6–39.8%) | 60.4% | 372/20 | 24.9% (17.4–33.2%) | 43.6% |
| 24 months | 155/12 | 39% (24.8–54%) | 63.8% | 119/11 | 29% (16.4–43.1%) | 51.3% |
| 36 months | 35/4 | 51.4% (33.1–69.6%) | 0% | 35/4 | 42.4% (24.7–60.9%) | 0% |
| **Quality score ≥7** | 485/19 | 27.4% (20.3–35%) | 55.9% | 458/19 | 21.5% (15.1–28.5) | 49.4% |

**Table III Complete response and disease recurrence after conservative management of early-stage endometrial cancer.**

| | Frequency | Percent | Valid percent |
|---|---|---|---|
| **Women undergoing CMEC**[a] | 861 | 100 | 100 |
| **Complete response** | | | |
| Yes | 682 | 79.2 | 79.7 |
| No | 174 | 20.2 | 20.3 |
| Missing | 5 | 0.6 | – |
| **Disease recurrence**[b] | | | |
| Yes | 235 | 34.5 | 35.3 |
| No | 430 | 63 | 64.7 |
| Missing | 17 | 2.5 | – |

CMEC, conservative management of endometrial cancer.
[a]Reviewed from 46 studies.
[b]Calculated among women with complete response.

proceeding from several countries were identified for data extraction and meta-analysis, leading to a sample exceeding 850 women. A stringent definition of EEC was adopted and, in addition to data on the study outcomes, several study-level variables were considered. The quality of each included study was evaluated with an *ad hoc* instrument, and additional moderator and sensitivity analyses investigated possible effect modifiers and the stability of the findings in subsets of studies.

Limitations are mainly related to the available data sources. Half of the included studies were categorized as case series and two-fifths of them included fewer than 10 eligible women. Apart from larger CIs and uncertainty, small case series are particularly vulnerable to selection and publication bias. These types of sources were expected because CMEC is a relatively new alternative, and potential candidates are underrepresented among women with endometrial cancer (Morice *et al.*, 2016). Nevertheless, moderator and sensitivity analyses showed stable findings when controlling for sample size, design or study quality. It should be noted that, since we specifically selected studies reporting on the reproductive outcomes, the descriptive findings on the oncological outcomes cannot be used to estimate the long-term impact of CMEC on recurrence and survival. A further limitation is the lack of detailed obstetric/perinatal data regarding the pregnancies after CMEC, although robust information was available regarding mode of conception (82.9% of reviewed pregnancies) and multiple births (78.2% of reviewed deliveries with live births). We are finally unable to make inferences regarding individual level prognostic factors for the outcomes, such as the BMI (Gonthier *et al.*, 2014), because of heterogeneity among/within studies and lack of individual participant data.

**Table IV Mode of conception and pregnancy outcome after conservative management of early-stage endometrial cancer.**

| | Frequency | Percent[a] | Valid percent[a] |
|---|---|---|---|
| **Pregnancies**[b] | 286 | 100 | 100 |
| **Mode of conception** | | | |
| Spontaneous | 79 | 27.6 | 33.3 |
| Fertility treatment | 158 | 55.2 | 66.7 |
| Missing | 49 | 17.1 | – |
| **Outcome** | | | |
| Pregnancy loss | 77 | 26.9 | 27.1 |
| Ongoing pregnancy | 10 | 3.5 | 3.5 |
| Delivery with live birth | 197 | 68.9 | 69.4 |
| Missing | 2 | 0.7 | – |
| **Multiple birth**[c] | | | |
| No | 140 | 71.1 | 90.9 |
| Twin | 11 | 5.6 | 7.1 |
| Triplet | 3 | 1.5 | 1.9 |
| Missing | 43 | 21.8 | – |

[a]Rounded to the 1st decimal.
[b]Reviewed from 44 studies with adequate data reporting.
[c]Calculated among deliveries with live birth.

## Interpretation

Endometrial cancer is a common malignancy and, although it mainly affects postmenopausal women, the number of women diagnosed during reproductive age is expected to grow (Rodolakis *et al.*, 2015; Hamilton *et al.*, 2021b). It is therefore not surprising that the possibility of avoiding or postponing iatrogenic absolute uterine factor infertility has gained popularity (La Russa *et al.*, 2018). The mainstay of most CMEC strategies is a medical treatment with progestins, which are potent agents against endometrial neoplasms as proved by high complete response rates in this and previous studies (Rodolakis *et al.*, 2015; La Russa *et al.*, 2018; Hamilton *et al.*, 2021b). Regardless of the direct effects of CMEC on the neoplasia, the intended outcomes of fertility preservation are pregnancies and, most importantly, live births. In other words, the reproductive outcomes are an ultimate measure of success for CMEC and should be kept in focus. This is particularly important because CMEC is considered as a temporary solution, and recurrence rates greater than 30% have been observed in the present and previous studies (Gallos *et al.*, 2012; Gunderson *et al.*, 2012). Besides, limited data on the long-term oncological safety of postponing the standard treatment in this specific group of women are available (Rodolakis *et al.*, 2015; Greenwald *et al.* 2017; Ruiz *et al.*, 2017; Hamilton *et al.*, 2021b). The chances of pregnancy and live birth estimated in our meta-analyses are to be weighed against the above-mentioned limitations, when considering CMEC for fertility preservation.

It should be noted that more optimistic findings have been highlighted in several individual studies, with chances of live birth approaching or exceeding 50% (Niwa *et al.*, 2005; Mao *et al.*, 2010; Wang *et al.*, 2015; Falcone *et al.*, 2017; Wang *et al.*, 2017; Maggiore *et al.*, 2019; Mazzon *et al.*, 2020; Atallah *et al.*, 2021). Differences across individual studies are consistent with the heterogeneity in our analyses and may relate to design and methodology as well as to selection or publication bias (Murad *et al.*, 2018). Heterogeneity appears to be related to prognostic features such as age. When restricting the meta-analysis to studies including women aged 35 or younger, higher chances of pregnancy and live birth, as well as low heterogeneity, were found. Another contributor to heterogeneity, as suggested by moderator and sensitivity analyses, is follow-up length, which varies greatly across studies yet predicts the reproductive outcomes.

A larger and updated evidence base explains discrepancies between the present and previous reviews (Gallos *et al.*, 2012; Gunderson *et al.*, 2012; Koskas *et al.*, 2014; Wei *et al.*, 2017; Fan *et al.*, 2018), although those may also relate to methodological choices. Inflated pregnancy rates exceeding 50% have been highlighted when selectively choosing women who responded to treatment as the denominator in the calculation (Fan *et al.*, 2018). In our study, all treated women were instead considered, in order to avoid survivorship bias and in analogy to the intention-to-treat principle of clinical trials. The inclusion of case reports (Gunderson *et al.*, 2012), which were instead excluded in our study, may also lead to larger estimates because of the indirect effect of publication bias. Inconsistency with our results may also be related to broader definitions of early-stage cancer (Gallos *et al.*, 2012) or to the inclusion of endometrial hyperplasia (Wei *et al.*, 2017), because of a plausible relation between disease type or severity and prognosis (Morice *et al.*, 2016).

## Implications

From a clinical perspective, our findings suggest CMEC as a viable alternative for young women with well-differentiated, Clinical Stage IA, endometrioid endometrial cancer who want to preserve their fertility, since pregnancy and live births will be possible for many of them. However, there still appears to be room for improvement as the main meta-analyses estimate that pregnancies and live births are achieved respectively by one out of four and one out of five treated women.

Regarding the treatment, either oral (MPA or MA) or intrauterine (levonorgestrel) progestins may be recommended as they are to date the most studied option (La Russa *et al.*, 2018; Hamilton *et al.*, 2021b). The combination of oral and intrauterine progestins has been proposed but there is insufficient evidence regarding its superiority over a single route of administration (Hamilton *et al.*, 2021b). Similarly, several authors have proposed hysteroscopic resection before progestin-based treatment (Wang *et al.*, 2014; 2015; Falcone *et al.*, 2017; Wang *et al.*, 2017; Casadio *et al.*, 2018; Giampaolino *et al.*, 2019; Yang *et al.*, 2019; Ayhan *et al.*, 2020; Casadio *et al.*, 2020; Mazzon *et al.*, 2020; Atallah *et al.*, 2021; Raffone *et al.*, 2021). This could be justified in view of our findings, the diagnostic-therapeutic value of hysteroscopy, and the limited costs or risks associated with the procedure. Besides, hysteroscopy appears to be associated with higher remission rates in these patient groups (Guillon *et al.*, 2019). However, hysteroscopy implementation may be challenging (Gambadauro *et al.*, 2018) and large randomized trials would be needed in order to evaluate the real effect gain. The use of metformin in addition to progestins has also been proposed for these patients (Yang *et al.*, 2020) and, although there is insufficient knowledge of its incremental effect on reproductive outcomes, it seems an interesting topic for future investigations.

The heterogeneity in our analyses suggests caution when counselling and selecting women for CMEC. Despite broad consensus regarding the main oncological criteria to be considered, it has not been discussed how each candidate's reproductive prognosis should be evaluated and used to support decision-making (Harrison et al., 2019; Gambadauro, 2020). Establishing valid selection criteria based on the reproductive prognosis is therefore a promising area for improvement. For instance, while simple markers such as age are certainly helpful, the role of an infertility work-up to improve the effectiveness of CMEC has not been examined. It is also important to note how a large proportion of pregnancies after CMEC are obtained through fertility treatments. Ovulation-stimulating drugs have been associated with endometrial cancer, but the evidence of an independent association seems inconclusive (Siristatidis et al., 2013; Skalkidou et al., 2017) and observational data could not show an increased risk of recurrence among women who underwent fertility treatments after CMEC (Park et al., 2013). This information should be part of the counselling and supports the need for close collaboration between oncologists and fertility specialists in designing individualized strategies (Gambadauro, 2020).

One final consideration concerns the time perspective of CMEC strategies, which is obviously important for both reproductive and oncological outcomes. The increased chances of pregnancy and live birth estimated among studies with longer follow-up are encouraging and to some extent expected, although these observations cannot be uncritically translated into clinical recommendations. Endpoints such as pregnancies and live births naturally require time to occur, but CMEC is conventionally offered as a temporary solution and there is uncertainty regarding the safest time to attempt pregnancy or the ideal timing of hysterectomy. Furthermore, female fertility decreases over time and many of these women are already in a critical phase of their reproductive years. Clearly, more knowledge is needed in order to achieve the best possible balance between the gain in live birth and the oncological risks of longer strategies. Since randomized comparisons of oncological outcomes between CMEC and the standard treatment are arguably not feasible, because they preclude the chance of conception for some of the participants, it seems mandatory to follow-up these women within lifelong prospective cohorts, ideally in the context of national or multinational registers. The potential threat of publication and survivorship bias should also be acknowledged because women with more favourable outcomes may for instance receive longer follow-ups or just seem more newsworthy than those with poorer outcomes. Population-based data from the USA show that, despite a growing implementation of CMEC in clinical settings, the proportion of women who eventually experience live birth is lower than 10% (Harrison et al., 2019). Although it is assumed that women who choose CMEC intend to subsequently pursue a pregnancy, there may be several unexplored reasons, medical or even social, for the apparent divide between what is observed in clinical trials and what happens after implementation in real-life settings. Translational efforts focusing on the long-term planning and surveillance of women undergoing CMEC are therefore needed.

### Conclusions

Conservative management based on progestins is viable for women with well-differentiated, Clinical Stage 1A, endometrioid endometrial cancer who want to preserve their fertility, but there is room for improvement as only one-fifth of them are estimated to achieve live birth according to this meta-analysis. Higher chances may be expected among younger women, when progestins are combined with hysteroscopic resection, or with longer follow-up. In addition, two-thirds of the pregnancies are medically assisted. Further investigations on prognosis-driven selection, hysteroscopic resection and long-term surveillance are arguably needed in order to improve the reproductive outcomes of CMEC.

## Supplementary data

Supplementary data are available at *Human Reproduction Update online*.

## Data availability

The data underlying this systematic review and meta-analysis are from previously published studies, which have been cited. Further data generated in support of this research are available in the article and in its online supplementary material.

## Authors' roles

E.H.C.: contribution to design, data acquisition, data analysis and interpretation, article drafting. J.H.: acquisition of data, interpretation, critical revision. R.T.: contribution to design, critical revision. P.G.: conception and design, data analysis and interpretation, article drafting. All authors approved the final version of the manuscript.

## Funding

Funding was received from The Family Planning Fund in Uppsala, Uppsala, Sweden (P.G.).

## Conflict of interest

The authors have no conflict of interest to disclose.

## References

Andress J, Pasternak J, Walter C, Kommoss S, Krämer B, Hartkopf A, Brucker SY, Schönfisch B, Steinmacher S. Fertility preserving management of early endometrial cancer in a patient cohort at the department of women's health at the university of Tuebingen. *Arch Gynecol Obstet* 2021;**304**:215–221.

Atallah D, El Kassis N, Safi J, El Hachem H, Chahine G, Moubarak M. The use of hysteroscopic endometrectomy in the conservative treatment of early endometrial cancer and atypical hiperplasia in fertile women. *Arch Gynecol Obstet* 2021;**304**:1299–1305.

Ayhan A, Tohma YA, Tunc M. Fertility preservation in early-stage endometrial cancer and endometrial intraepithelial neoplasia: a

single-center experience. *Taiwan J Obstet Gynecol* 2020;**59**: 415–419.

Bower B, Quinn GP. Fertility preservation in cancer patients: ethical considerations. *Adv Exp Med Biol* 2012;**732**:187–196.

Cade TJ, Quinn MA, Rome RM, Neesham D. Long-term outcomes after progestogen treatment for early endometrial cancer. *Aust N Z J Obstet Gynaecol* 2013;**53**:566–570.

Casadio P, Guasina F, Paradisi R, Leggieri C, Caprara G, Seracchioli R. Fertility-sparing treatment of endometrial cancer with initial infiltration of myometrium by resectoscopic surgery: a pilot study. *Oncologist* 2018;**23**:478–480.

Casadio P, La Rosa M, Alletto A, Magnarelli G, Arena A, Fontana E, Fabbri M, Giovannico K, Virgilio A, Raimondo D *et al*. Fertility sparing treatment of endometrial cancer with and without initial infiltration of myometrium: a single center experience. *Cancers* 2020; **12**:3571.

Center for Evidence Synthesis in Health (CESH). Software [Internet]. USA: Brown University, School of Public Health; 2021. https://www.brown.edu/public-health/cesh/resources/software (12 July 2021, date last accessed).

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. *Int J Gynaecol Obstet* 2016;**132**:34–38.

Choi MC, Jung SG, Park H, Cho YH, Lee C, Kim SJ. Fertility preservation via photodynamic therapy in young patients with early-stage uterine endometrial cancer: a long-term follow-up study. *Int J Gynecol Cancer* 2013;**23**:698–704.

Constantine GD, Kessler G, Graham S, Goldstein SR. increased incidence of endometrial cancer following the women's health initiative: an assessment of risk factors. *J Womens Health (Larchmt)* 2019;**28**:237–243.

Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. *Gynecol Oncol* 2001;**83**:388–393.

Falcone F, Laurelli G, Losito S, Di Napoli M, Granata V, Greggi S. Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer. *J Gynecol Oncol* 2017;**28**:e2.

Fan Z, Li H, Hu R, Liu Y, Liu X, Gu L. Fertility-preserving treatment in young women with grade 1 presumed stage IA endometrial adenocarcinoma: a meta-analysis. *Int J Gynecol Cancer* 2018;**28**: 385–393.

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 meta-analysis. *Am J Obstet Gynecol* 2012;**207**:266.e1–266.e12.

Gambadauro P. The reproductive prognosis of women considering fertility preservation for early stage endometrial cancer. *Arch Gynecol Obstet* 2020;**302**:1305–1306.

Gambadauro P, Gudmundsson J. Endometrial cancer in a woman undergoing hysteroscopy for recurrent IVF failure. *Gynecol Surg* 2017; **14**:4.

Gambadauro P, Milenkovic M, Hadlaczky G. Simulation for training and assessment in hysteroscopy: a systematic review. *J Minim Invasive Gynecol* 2018;**25**:963–973.

Giampaolino P, Di Spiezio Sardo A, Mollo A, Raffone A, Travaglino A, Boccellino A, Zizolfi B, Insabato L, Zullo F, De Placido G *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. *J Minim Invasive Gynecol* 2019;**26**:648–656.

Gonthier C, Walker F, Luton D, Yazbeck C, Madelenat P, Koskas M. Impact of obesity on the results of fertility-sparing management for atypical hyperplasia and grade 1 endometrial cancer. *Gynecol Oncol* 2014;**133**:33–37.

Greenwald ZR, Huang LN, Wissing MD, Franco EL, Gotlieb WH. Does hormonal therapy for fertility preservation affect the survival of young women with early-stage endometrial cancer? *Cancer* 2017;**123**:1545–1554.

Guillon S, Popescu N, Phelippeau J, Koskas M. A systematic review and meta-analysis of prognostic factors for remission in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma. *Int J Gynecol Obstet* 2019;**146**: 277–288.

Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. *Gynecol Oncol* 2012;**125**:477–482.

Gungor T, Cetinkaya N, Yalcin H, Zergeroglu S, Erkaya S. Clinicopathologic characteristics and treatment features of women with the incidental diagnosis of endometrial adenocarcinoma during infertility follow-up in Ankara, Turkey. *Taiwan J Obstet Gynecol* 2016;**55**:309–313.

Hamilton CA, Pothuri B, Arend RC, Backes FJ, Gehrig PA, Soliman PT, Thompson JS, Urban RR, Burke WM. Endometrial cancer: a society of gynecologic oncology evidence-based review and recommendations. *Gynecol Oncol* 2021a;**160**:817–826.

Hamilton CA, Pothuri B, Arend RC, Backes FJ, Gehrig PA, Soliman PT, Thompson JS, Urban RR, Burke WM. Endometrial cancer: a society of gynecologic oncology evidence-based review and recommendations, part II. *Gynecol Oncol* 2021b;**160**: 827–834.

Harrison RF, He W, Fu S, Zhao H, Sun CC, Suidan RS, Woodard TL, Rauh-Hain JA, Westin SN, Giordano SH *et al*. National patterns of care and fertility outcomes for reproductive-aged women with endometrial cancer or atypical hyperplasia. *Am J Obstet Gynecol* 2019;**221**:474.e1–474.e11.

Imai M, Jobo T, Sato R, Kawaguchi M, Kuramoto H. Medroxyprogesterone acetate therapy for patients with adenocarcinoma of the endometrium who wish to preserve the uterus-usefulness and limitations. *Eur J Gynaecol Oncol* 2001;**22**:217–220.

Kaku T, Yoshikawa H, Tsuda H, Sakamoto A, Fukunaga M, Kuwabara Y, Hataeg M, Kodama S, Kuzuya K, Sato S *et al*. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. *Cancer Lett* 2001;**167**:39–48.

Kataoka H, Mori T, Yamamoto T, Sawada M, Kuroboshi M, Tatsumi H, Iwasaku K, Kitawaki J. Outcome of fertility-sparing treatment with medroxyprogesterone acetate for atypical hyperplasia and endometrial carcinoma in young Japanese women. *Eur J Gynaec Oncol* 2014;**35**:11–15.

Kim MK, Seong SJ, Kim YS, Song T, Kim M-L, Yoon BS, Jun HS, Lee YH. Combined medroxyprogesterone acetate/levonorgestrelein-trauterine system treatment in young women with early-stage endometrial cancer. *Am J Obstet Gynecol* 2013;**209**:358.e1–358.e4.

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 Res* 2012;**32**:1037–1044.

Koskas M, Uzan J, Luton D, Rouzier R, Daraï E. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. *Fertil Steril* 2014;**101**:785–794.

Kudesia R, Singer T, Caputo TA, Holcomb KM, Kligman I, Rosenwaks Z, Gupta D. Reproductive and oncologic outcomes after progestin therapy for endometrial complex atypical hyperplasia or carcinoma. *Am J Obstet Gynecol* 2014;**210**:255.e1–255.e4.

La Russa M, Zapardiel I, Halaska MJ, Zalewski K, Laky R, Dursun P, Lindquist D, Sukhin V, Polterauer S, Biliatis I. Conservative management of endometrial cancer: a survey amongst European clinicians. *Arch Gynecol Obstet* 2018;**298**:373–380.

Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International patterns and trends in endometrial cancer incidence, 1978-2013. *J Natl Cancer Inst* 2018;**110**:354–361.

Maggiore ULR, Martinelli F, Dondi G, Bogani G, Chiappa V, Evangelista MT, Liberale V, Ditto A, Ferrero S, Raspagliesi F. Efficacy and fertility outcomes of levonorgestrel-releasing intrauterine system treatment for patients with atypical complex hyperplasia or endometrial cancer: a retrospective study. *J Gynecol Oncol* 2019;**30**:e57.

Mao Y, Wan X, Chen Y, Lv W, Xie X. Outcomes of conservative therapy for young women with early endometrial adenocarcinoma. *Fertil Steril* 2010;**93**:283–285.

Mazzon I, Masciullo V, Scambia G, Ferrandina G, Corrado G. Long-term survival of young endometrial cancer patients desiring fertility preservation treated with hysteroscopic resection followed by hormone therapy (NEMO technique). *Int J Gynaecol Obstet* 2020;**151**:305–307.

Minaguchi T, Nakagawa S, Takazawa Y, Nei T, Horie K, Fujiwara T, Osuga Y, Yasugi T, Kugu K, Yano T *et al.* Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. *Cancer Lett* 2007;**248**:112–122.

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. *Ann Oncol* 2011;**22**:643–649.

Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.

Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. *Lancet* 2016;**387**:1094–1108.

Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018;**23**:60–63.

National Institute for Health Research (NIHR). PROSPERO, International prospective register of systematic reviews [Internet]. UK: University of York, Centre for Reviews and Dissemination; 2021. https://www.crd.york.ac.uk/PROSPERO/ (12 July 2021, date last accessed).

Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. *BJOG* 2005;**112**:317–320.

Ohyagi-Hara C, Sawada K, Aki I, Mabuchi S, Kobayashi E, Ueda Y, Yoshino K, Fujita M, Tsutsui T, Kimura T. 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. *Arch Gynecol Obstet* 2015;**291**:151–157.

Ota T, Yoshida M, Kimura M, Kinoshita K. Clinicopathologic study of uterine endometrial carcinoma in young women aged 40 years and younger. *Int J Gynecol Cancer* 2005;**15**:657–662.

Park J-Y, Seong SJ, Kim T-J, Kim JW, Kim SM, Bae D-S, Nam J-H. Pregnancy outcomes after fertility-sparing management in young women with early endometrial cancer. *Obstet Gynecol* 2013;**121**:136–142.

Parlakgumus HA, Kilicdag EB, Simsek E, Haydardedeoglu B, Cok T, Aytac PC, Bagis T, Erkanli S. Fertility outcomes of patients with early stage endometrial carcinoma. *J Obstet Gynaecol Res* 2014;**40**:102–108.

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. *Gynecol Endocrinol* 2012;**28**:559–561.

Perri T, Korach J, Gotlieb WH, Beiner M, Meirow D, Friedman E, Ferenczy A, Ben-Baruch G. Prolonged conservative treatment of endometrial cancer patients: more than 1 pregnancy can be achieved. *Int J Gynecol Cancer* 2011;**21**:72–78.

Raffone A, Travaglino A, Flacco ME, Iasevoli M, Mollo A, Guida M, Insabato L, Sardo ADS, Carugno J, Zullo F. Clinical predictive factors of response to treatment in patients undergoing conservative management of atypical endometrial hyperplasia and early endometrial cancer. *J Adolesc Young Adult Oncol* 2021;**10**:193–201.

Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, Gabra H, Paraskevaidis E, Martin-Hirsch P, Tsilidis KK, Kyrgiou M. Risk factors for endometrial cancer: an umbrella review of the literature. *Int J Cancer* 2019;**145**:1719–1730.

Rodolakis A, Biliatis I, Morice P, Reed N, Mangler M, Kesic V, Denschlag D. European society of gynecological oncology task force for fertility preservation: clinical recommendations for fertility-sparing management in young endometrial cancer patients. *Int J Gynecol Cancer* 2015;**25**:1258–1265.

Ruiz MP, Huang Y, Hou JY, Tergas AI, Burke WM, Ananth CV, Neugut AI, Hershman DL, Wright JD. All-cause mortality in young women with endometrial cancer receiving progesterone therapy. *Am J Obstet Gynecol* 2017;**217**:669.e1–669.e13.

Schünemann JH, Cook D, Guyatt G. Methodology for antithrombotic and thrombolytic therapy guideline development: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;**133**:113S–122S.

Shan B, Ren Y, Sun J, Tu X, Jiang Z, Ju X, Zang R, Wang H. A prospective study of fertility-sparing treatment with megestrol acetate

following hysteroscopic curettage for well-differentiated endometrioid carcinoma and atypical hyperplasia in young women. *Arch Gynecol Obstet* 2013;**288**:1115–1123.

Shirali E, Yarandi F, Eftekhar Z, Shojaei Z, Khazaeipour Z. Pregnancy outcome in patients with stage 1a endometrial adenocarcinoma, who conservatively treated with megestrol acetate. *Arch Gynecol Obstet* 2012;**285**:791–795.

Shobeiri MJ, Gharabaghi PM, Esmaeili H, Ouladsahebmadarek E, Mehrzad-Sadagiani M. Fertility sparing treatment in young patients with early endometrial adenocarcinoma. *Pak J Med Sci* 2013;**29**: 651–655.

Siristatidis C, Sergentanis TN, Kanavidis P, Trivella M, Sotiraki M, Mavromatis I, Psaltopoulou T, Skalkidou A, Petridou ET. Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer—a systematic review and meta-analysis. *Hum Reprod Update* 2013;**19**:105–123.

Skalkidou A, Sergentanis TN, Gialamas SP, Georgakis MK, Psaltopoulou T, Trivella M, Siristatidis CS, Evangelou E, Petridou E. Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. *Cochrane Database Syst Rev* 2017;**3**:CD010931.

Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. *ANZ J Surg* 2003; **73**:712–716.

Tamauchi S, Kajiyama H, Utsumi F, Suzuki S, Niimi K, Sakata J, Mizuno M, Shibata K, Kikkawa F. Efficacy of medroxyprogesterone acetate treatment and retreatment for atypical endometrial hyperplasia and endometrial cancer. *J Obstet Gynaecol Res* 2018;**44**:151–156.

Tock S, Jadoul P, Squifflet J-L, Marbaix E, Baurain J-F, Luyckx M. Fertility sparing treatment in patients with early stage endometrial cancer, using a combination of surgery and gnrh agonist: a monocentric retrospective study and review of the literature. *Front Med (Lausanne)* 2018;**5**:1–10.

Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, Nakanishi T, Sasaki H, Saji F, Iwasaka T *et al*. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. *J Clin Oncol* 2007;**25**:2798–2803.

Wang C-J, Chao A, Yang L-Y, Hsueh S, Huang Y-T, Chou H-H, Chang T-C, Lai C-H. Fertility-preserving treatment in young women with endometrial adenocarcinoma: a long-term cohort study. *Int J Gynecol Cancer* 2014;**24**:718–728.

Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw* 2012;**49**:1–15.

Wang Q, Guo Q, Gao S, Xie F, Du M, Dong J, Sui L, Xie K. Fertility-conservation combined therapy with hysteroscopic resection and oral progesterone for local early stage endometrial carcinoma in young women. *Int J Clin Exp Med* 2015;**8**:13804–13810.

Wang F, Yu A, Xu H, Zhang X, Li L, Lou H, Yu H, Lin J. Fertility preserved hysteroscopic approach for the treatment of stage IA endometrioid carcinoma. *Int J Gynecol Cancer* 2017;**27**:1919–1925.

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 (United States)* 2017;**96**:1–9.

Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. The Ottawa Hospital, Research Institute; 2021. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (12 July 2021, date last accessed).

Yamagami W, Susumu N, Makabe T, Sakai K, Nomura H, Kataoka F, Hirasawa A, Banno K, Aoki D. Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility? *J Gynecol Oncol* 2018;**29**:e21.

Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, Shozu M, Isaka K. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. *Hum Reprod* 2007;**22**:1953–1958.

Yang BY, Gulinazi Y, Du Y, Ning CC, Cheng YL, Shan WW, Luo XZ, Zhang HW, Zhu Q, Ma FH *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* 2020;**127**:848–857.

Yang H-C, Liu J-C, Liu F-S. Fertility-preserving treatment of stage IA, well-differentiated endometrial carcinoma in young women with hysteroscopic resection and high-dose progesterone therapy. *Taiwan J Obstet Gynecol* 2019;**58**:90–93.

Yu M, Yang J-X, Wu M, Lang J-H, Huo Z, Shen K. Fertility-preserving treatment in young women with well-differentiated endometrial carcinoma and severe atypical hyperplasia of endometrium. *Fertil Steril* 2009;**92**:2122–2124.

Zhang Z, Huang H, Feng F, Wang J, Cheng N. A pilot study of gonadotropin-releasing hormone agonist combined with aromatase inhibitor as fertility-sparing treatment in obese patients with endometrial cancer. *J Gynecol Oncol* 2019;**30**:e61.

Zhou R, Yang Y, Lu Q, Wang J, Miao Y, Wang S, Wang Z, Zhao C, Wei L. 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. *Gynecol Oncol* 2015;**139**:424–428.