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REVIEW ARTICLE

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The oncological and reproductive outcomes of fertility-preserving treatments for stage 1 grade 1 endometrial carcinoma: a systematic review and meta-analysis

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ABSTRACT

Introduction: The number of patients desiring fertility-preserving treatment for endometrial cancer rather than standard surgical management continues to increase.

Objective: We aimed to evaluate the efficacies of fertility-preserving treatments on the live birth rate, remission and relapse rates for women with stage 1a grade 1 endometrial carcinoma to support patient counselling.

Methods: We performed a meta-analysis for our primary outcomes of overall remission and relapse rate, and for secondary analysis, we divided papers into treatment type: systemic progestins, intrauterine progestins or hysteroscopic resection and adjuvant hormonal treatment.

Results: Thirty-five observational studies met inclusion criteria, with a total of 624 patients. Overall, conservative treatment of endometrial cancer showed a remission rate of 77% (95% CI: 70–84%), a relapse rate of 20% (95% CI: 13–27%) and a live birth rate of 20% (95% CI: 15–25%) with more favourable outcomes for the hysteroscopic resection group.

Conclusions: Hysteroscopic resection and adjuvant hormonal treatment had the most favourable fertility and oncological outcomes. Further high-quality prospective multi-centre trials are warranted to determine the optimal treatment regimen and dosage and risk stratification for these patients.

PLAIN LANGUAGE SUMMARY

The number of women diagnosed with womb cancer who want to preserve their fertility is increasing. Traditional treatment involves surgery to remove the womb and ovaries, rendering women infertile. Fertility-preserving treatments (e.g. hormone therapy, removing only affected areas) exist but their impact on remission, relapse and fertility is not certain. Our team discovered that for women who underwent fertility-preserving treatment: three in four had cancer remission, one in five had cancer relapse and one in five had a successful birth. More research is needed to work out the best fertility-preserving treatment and identify which women are more likely to have successful pregnancies.

Overall, our research will help to counsel women diagnosed with womb cancer who want to preserve their fertility or are unsuitable for major surgery more effectively.

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KEYWORDS
Endometrial cancer; fertility preserving; progesterone; hysteroscopic resection

Introduction

Endometrial carcinoma (EC) is increasing in incidence, affecting 9400 women/year in the United Kingdom (Cancer Research UK 2020), primarily driven by a growing obesity epidemic (Raglan *et al.* 2019). In the UK, 3% of women are below 45 years of age at diagnosis (Cancer Research UK 2020), with worldwide estimates at 5–7% (Duska *et al.* 2001, Siegel *et al.* 2016, Obermair *et al.* 2020).

Standard surgical management for low-risk tumours comprises total hysterectomy and bilateral salpingo-oophorectomy, with consideration of pelvic lymph-node assessment (Morrison *et al.* 2021). This has excellent survival outcomes (Lajer *et al.* 2012), at the expense of fertility and endocrine function. Women of reproductive-age have lower-stage disease and better stage-specific survival than older women (Lee *et al.* 2007). With women increasingly delaying childbearing (Age of Women Giving Birth 2021), many may wish to conserve their reproductive potential and choose fertility-preserving treatments. Non-surgical treatments also have a role for women with significant comorbidities (Terzic *et al.* 2020), although this will not be discussed further here.

Fertility-preserving treatments include progestins, oral (megestrol acetate (MA), medroxyprogesterone acetate (MPA)) and intrauterine (levonorgestrel–intrauterine-system (LNG-IUS)), and gonadotropin-releasing hormone analogs (GnRHa) (Terzic *et al.* 2020). Hysteroscopic resection may be

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used, usually prior to further hormonal treatment (Alonso *et al.* 2015), which is distinct from hysteroscopic biopsy for diagnosis. The risks of fertility-sparing management options include under-staging of disease and a higher risk of disease progression/relapse, which may ultimately require hysterectomy (Alonso *et al.* 2015). There may be failure to achieve a live-birth despite these risks.

EC guidelines from the British Gynaecological Cancer Society (BGCS) (Morrison *et al.* 2021) and Europe (Concin *et al.* 2021) permit fertility-preserving approaches in selected grade 1/stage 1a EC cases, after careful counselling with regular follow-up. The recommended management is high-dose oral MPA/MA, or consideration of IUS with/without GnRHa. The paucity of data on fertility and oncological outcomes is highlighted, which currently limits confidence in counselling.

There is therefore a need for an updated and comprehensive systematic review of both reproductive and oncological outcomes, focusing on stage 1a/grade 1 EC, reflecting recommended clinical practice.

This paper aims to update the literature by evaluating the efficacies of fertility-preserving EC treatments. The population is reproductive-age women with stage 1a/grade 1 EC desiring fertility. The outcomes are rates of remission, relapse and live-births. A secondary aim is to assess outcomes by treatment-modality where possible.

Methods

Literature search

A systematic review of the following databases was conducted: Medline, Embase, Central, Cochrane, NICE and Web of Science, from database inception to October 2020, for English language publications.

Medical subject headings (MeSH) and free text were combined to generate a subset of citations including studies with endometrial cancer ('endometr* neoplasm', 'endometr* cancer') and another subset of fertility-preserving treatments ('fertility preserv', fertility 'sparing', 'live birth', 'pregnancy'), and these subsets were combined. Previous literature reviews were examined for any references not included by the above search strategy.

The population of interest was women with International Federation of Gynecology and Obstetrics (FIGO) stage Ia grade 1 endometrial adenocarcinoma, who desire fertility-preserving treatment. Stage 1A is defined as a tumour confined to the endometrium or less than one-half of the myometrium (Lewin 2011). Grade 1 is defined by well differentiated cells (Lewin 2011). The interventions were fertility preserving treatments, such as progestins (systemic/intrauterine), GnRH analogues, hysteroscopic resection or others, in any combination. The outcomes were rates of remission (proportion of all patients who achieved complete response to treatment), relapse (proportion of all patients who relapsed after achieving remission) and of women achieving a live-birth. We did not pre-specify a timeframe for follow-up in our inclusion criteria but recorded this for all studies.

This study was prospectively registered with PROSPERO (CRD42021239714), with a protocol detailing the review question, search strategy, inclusion/exclusion criteria, risk-of-bias assessment and meta-analysis with a plan for assessment of heterogeneity. This review has been conducted in accordance with the AMSTAR-2 criteria (Shea *et al.* 2017).

Study selection and data extraction

Studies were selected if the participants were women with histologically diagnosed grade 1 EC, presumed stage 1a, who underwent fertility-preserving treatments with the purpose of preserving fertility, for the treatment of primary EC. The primary outcomes were rates of live birth, remission and relapse. Both non-randomised (e.g. case reports, observational studies) and randomised studies were included in our review reflecting the available evidence, with very few randomised studies in this field. Exclusion criteria were: not involving stage 1a grade 1 endometrial adenocarcinoma, not involving fertility-preserving treatments, not reporting primary outcomes of interest, review articles, letters and literature that did not provide original data or detailed treatment methods. Case series of fewer than five patients were excluded in order to ensure that centres managing such patients had sufficient experience, and better enable meta-analysis. Conference abstracts were suitable for inclusion if they provided all necessary information.

Two authors (SO and RG) independently screened titles and abstracts. Following this, full texts of shortlisted abstracts were retrieved to assess eligibility for inclusion. Any disagreements between these reviewers were settled by a third reviewer (AO). All duplicates were removed; in cases where the same group had multiple publications with overlapping patient groups, the most recent or complete publication was used, or data combined where it was clearly possible to do so (e.g. where a later publication provided longer-term follow-up data for the same patient group). All excluded papers were coded with a justification for their exclusion from the review.

Baseline characteristics and outcome data were extracted for each study by two authors (SO and OO), achieving consensus, into a table in Microsoft Excel (Microsoft Corporation 2018, Redmond, WA). The following data were extracted from each study: population (including median age of patients), study setting, intervention(s), including doses where required, length of follow-up (in months), number of patients, number of patients who achieved complete remission, number of patients who relapsed after complete remission, number of patients who achieved a live birth, and deaths. Rates were calculated for complete remission, relapse and total number of patients who achieved a live birth (number of patients who achieved a live birth divided by total number of patients). This definition of live birth rate was chosen as this reflects what would be of most clinical value to patients.

Risk of bias assessment

A risk of bias assessment using the Methodological Index for Non-Randomised Studies (MINORS) (Slim *et al.* 2003) was

conducted by two authors working independently (OO and SO), on all included papers. The items were scored 0 if not reported; 1 when reported but inadequate; and 2 when reported and adequate. The global ideal score is 16 for the included studies.

Statistical analysis

JASP version 0.14.1 (JASP software) (JASP Team 2020) was used for statistical analysis. Remission rates, relapse rates and live-birth rates were extracted from each study. Differences in rates with 95% confidence intervals were calculated for each study and for the summary effects. Statistical heterogeneity was assessed with I^2 tests and where I^2 was greater than 50% results were considered to have significant heterogeneity and a random-effects model was used; otherwise, a fixed-effects model was used.

Results

Study selection

The initial search yielded 367 abstracts, of which 125 were duplicates, leaving 242 abstracts remaining. From 1946 to October 2020, 35 eligible articles were included, with a total of 675 patients across 12 countries (see Figure 1 for a flow diagram). Three primary treatment groups were identified: 441 patients treated with oral progesterone only, 126 patients treated with hysteroscopic resection and adjuvant progestin therapy and 57 patients treated with intrauterine progesterones (LNG-IUS) and adjuvant progesterone therapy. Of the 51 patients not delineated into one of the three groups: one study (14 patients) described intra-uterine photodynamic therapy (Choi 2013) and two studies (37 patients) did not report fertility and mortality outcomes for each treatment group (Perri 2011, Kudesia 2014).

Risk of bias assessment

The risk of bias assessment using the MINORS checklist (Slim *et al.* 2003) is shown in Table S1. The majority of the studies had a clearly stated aim (34 of 35), included consecutive patients (21 of 35) and appropriate endpoints (33 of 35). Over half were prospective cohort studies (21 of 35). Only one study had blinded assessment of outcomes. We defined appropriate follow-up to be at least 5 years (Gallos *et al.* 2012), and this was satisfied in only nine of 35 studies. No studies had a loss to follow up of >5%.

Overall results

Thirty-five studies were included in our review, involving 675 patients from 12 countries (Randall and Kurman 1997, Gotlieb *et al.* 2003, Niwa *et al.* 2005, Yahata *et al.* 2006, Minaguchi *et al.* 2007, Ushijima *et al.* 2007, Yamazawa *et al.* 2007, Hahn *et al.* 2009, Han *et al.* 2009, Yu *et al.* 2009, Mao *et al.* 2010, Mazzon *et al.* 2010, Minig *et al.* 2011, Perri *et al.* 2011, Koskas *et al.* 2012, H. Park *et al.* 2012, Pashov *et al.* 2012, Cade *et al.* 2013, Choi *et al.* 2013, Kim *et al.* 2013, J.-Y. Park *et al.* 2013b, 2013a, B.-E. Shan *et al.* 2013, Shobeiri *et al.* 2013, Kudesia *et al.* 2014, Parlakgumus *et al.* 2014, C.-J. Wang *et al.* 2014, Ohyagi-Hara *et al.* 2015, Q. Wang *et al.* 2015, Falcone *et al.* 2017, Fukui *et al.* 2017, F. Wang *et al.* 2017, Tamauchi *et al.* 2018, Giampaolino *et al.* 2019, H.-C. Yang *et al.* 2019). The median ages and median length of follow

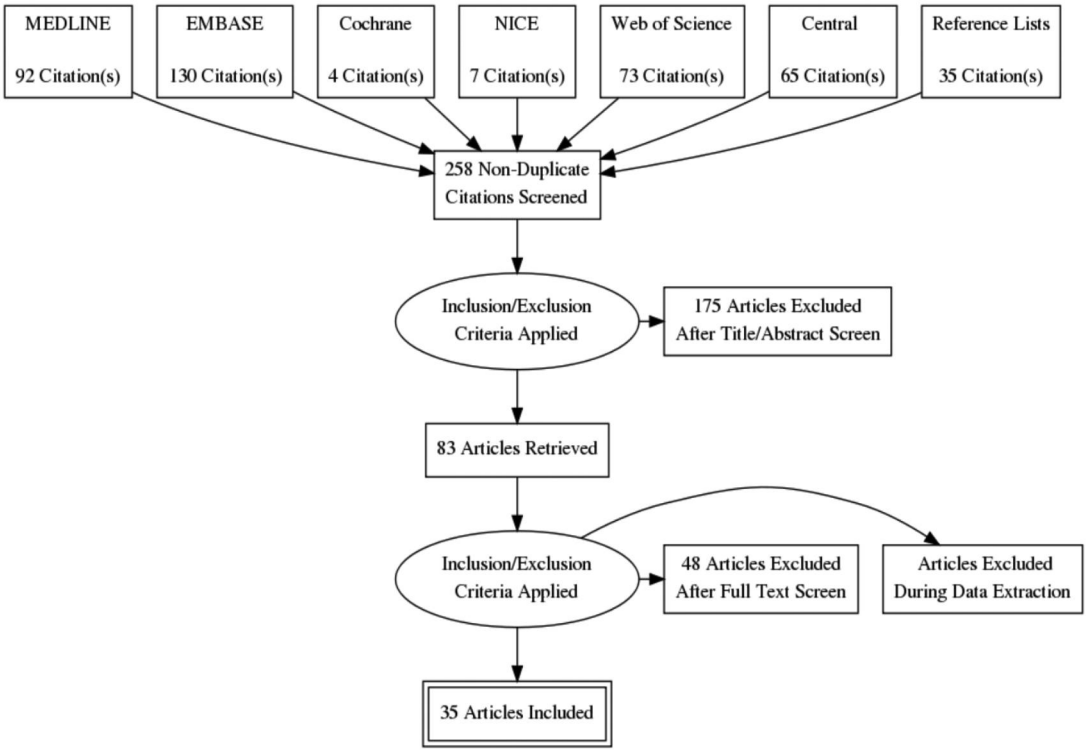

Figure 1. PRISMA flow diagram.

up are reported in Table S2. Due to similarity of patient population, study type and outcomes reported, combination of data into a meta-analysis was undertaken for overall results and by treatment type. Meta-analysis of all included studies found the fertility-preserving therapies had a combined remission rate of 77% (95% CI: 70–84%) with an I^2 value of 0.0%, indicating low heterogeneity (Figure 2(A)). The combined relapse rate of 20% (95% CI: 13–27%) with I^2 of 88% indicating significant heterogeneity (Figure 2(B)). The proportion of women achieving a live birth was 20% (95% CI: 15–25%) with I^2 of 59% indicating significant heterogeneity among studies (Figure 2(C)). The number of women actively trying to conceive after complete remission was not consistently reported, nor was the proportion receiving assisted reproductive treatments, and so reliable summary data for these could not be described.

Oral progestins

Nineteen studies containing 441 patients reported primary treatment with oral progestin therapy (Randall and Kurman 1997, Gotlieb *et al.* 2003, Niwa *et al.* 2005, Yahata *et al.* 2006, Minaguchi *et al.* 2007, Ushijima *et al.* 2007, Yamazawa *et al.* 2007, Hahn *et al.* 2009, Han *et al.* 2009, Yu *et al.* 2009, Mao *et al.* 2010, Koskas *et al.* 2012, H. Park *et al.* 2012, J.-Y. Park *et al.* 2013b, 2013a, Shobeiri *et al.* 2013, Ohyagi-Hara *et al.* 2015, Fukui *et al.* 2017, Tamauchi *et al.* 2018). These included MPA (20–1000 mg), MA (10–400 mg), norethisterone acetate (5 mg), nomegestrol acetate (5 mg) and hydroxyprogesterone caproate (doses not disclosed). The complete remission rate was 76% (95% CI: 67–84%) (Figure 3(A)). The I^2 value was 0.0%, indicating no observed heterogeneity among studies. Of those who achieved complete remission, there was a relapse rate of 28% (95% CI: 17–39%) (Figure 3(B)), The I^2 value was 86%, indicating significant heterogeneity among studies. The live birth rate was 17% (95% CI: 14–21%) (Figure 3(C)). The I^2 value was 48%, indicating no significant heterogeneity among the studies.

Hysteroscopic resection and adjuvant progestin

Nine studies containing 126 patients reported on hysteroscopic resection with adjuvant progestins (Yu *et al.* 2009, Mazzon *et al.* 2010, B.-E. Shan *et al.* 2013, Parlakgumus *et al.* 2014, C.-J. Wang *et al.* 2014, Q. Wang *et al.* 2015, Falcone *et al.* 2017, F. Wang *et al.* 2017, Giampaolino *et al.* 2019). Adjuvant progestins included oral MA (80–320 mg daily)/MPA (250–500 mg daily)/oral dydrogesterone (10 mg daily), or the LNG-IUS (20 μg daily). The complete remission rate was 84% (95% CI: 68–100%) (Figure 3(D)). The I^2 value was 0.0%, indicating no observed heterogeneity among studies. Of those who achieved complete remission, there was a relapse rate of 9.3% (95% CI: 0.0–18%) (Figure 3(E)), The I^2 value was 70%, indicating significant heterogeneity among studies. Among the patients who achieved complete remission, the live birth rate was 22% (95% CI: 7.0–38%) (Figure 3(F)), the I^2 value was 83%, indicating significant heterogeneity among the studies.

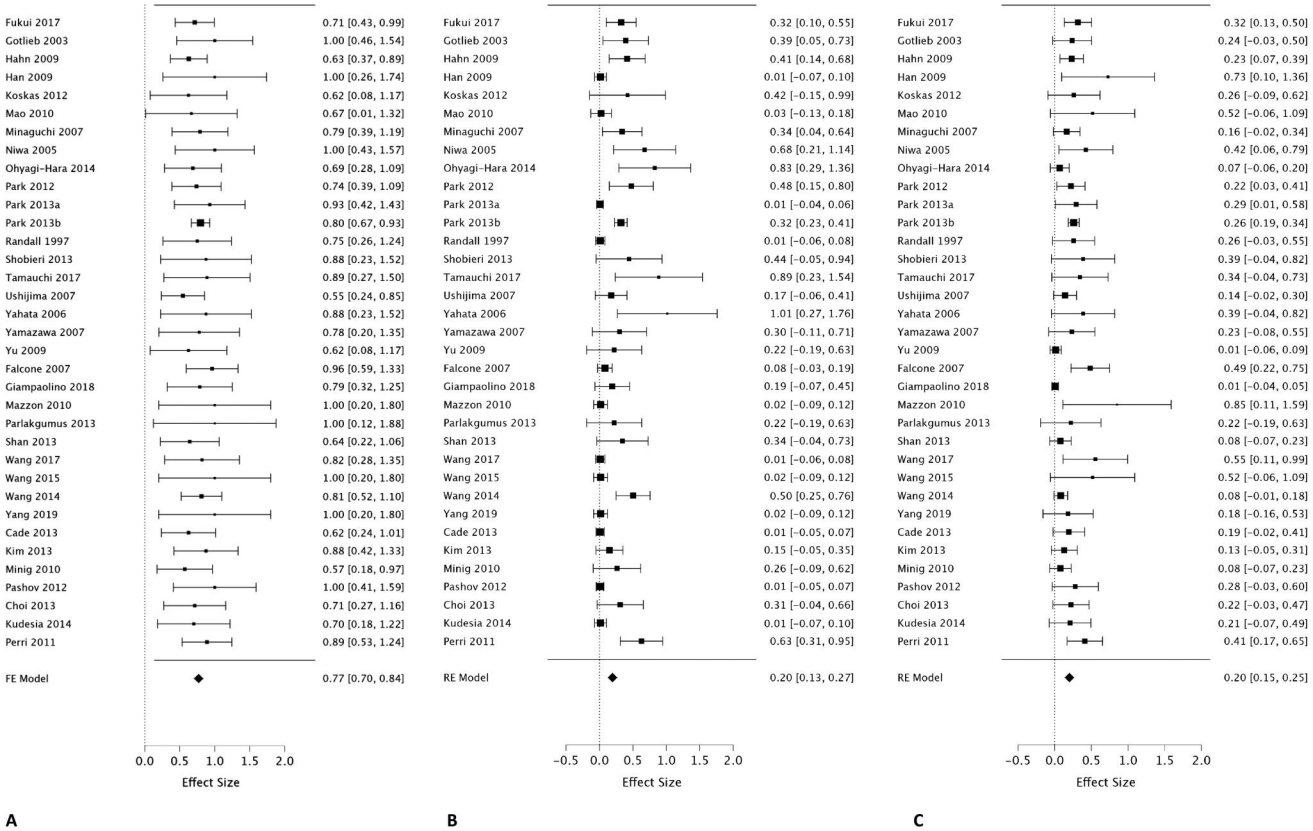

Figure 2. Remission rate (A), relapse rate (B) and proportion of live births (C) following fertility-preserving treatment in endometrial cancer.

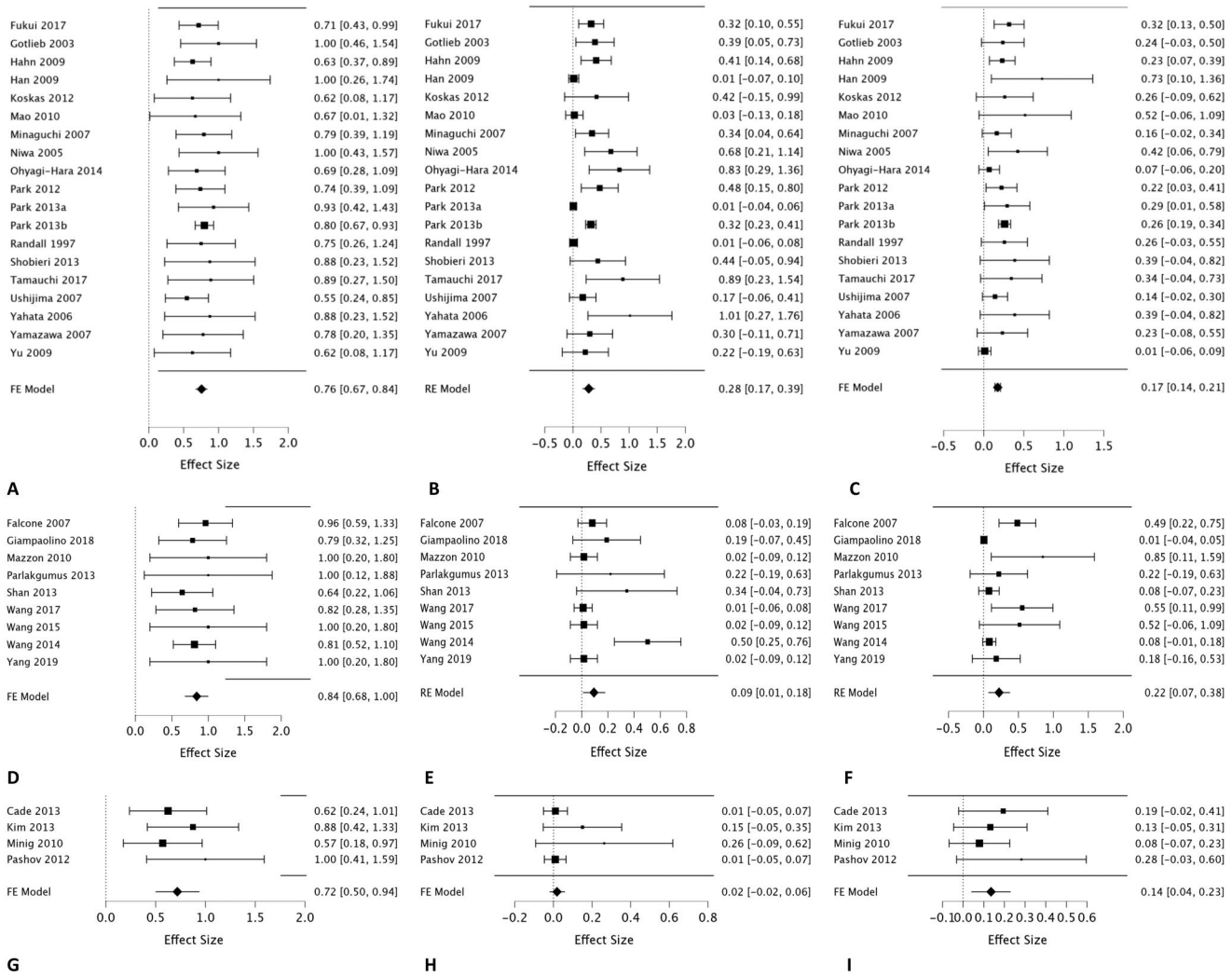

Figure 3. Remission rate (A), relapse rate (B) and proportion of live births (C) following oral progesterone therapy. Remission rate (D), relapse rate (E) and proportion of live births (F) following hysteroscopic resection and adjuvant progesterone therapy. Remission rate (G), relapse rate (H) and proportion of live births (I) following intrauterine progesterone therapy.

Intrauterine progestins and adjuvant hormonal therapy

Four studies containing 57 patients reported using the LNG-IUS (20 μg daily) alongside systemic progestins including oral MA (400–500 mg daily), or intramuscular GnRH analogues (leuprorelin acetate 3.75 mg monthly) (Minig *et al.* 2011, Pashov *et al.* 2012, Cade *et al.* 2013, Kim *et al.* 2013). The complete remission rate was 72% (95% CI: 50–94%) (Figure 3(G)). The I^2 value was 0.0%, indicating no observed heterogeneity among studies. Of those who achieved complete remission, there was a relapse rate of 2.1% (95% CI: 0.0–5.9%) (Figure 3(H)). The I^2 value was <0.1%, indicating no observed heterogeneity among studies. The live birth rate was 14% (95% CI: 4.0–23%) (Figure 3(I)), the I^2 value was 0.0%, indicating no significant heterogeneity among the studies (Figure 3(I)).

Discussion

This systematic review and meta-analysis provides a comprehensive summary of the evidence regarding oncological and reproductive outcomes following different fertility-preserving managements for stage 1a grade 1 EC. These data show that fertility-sparing management of EC results in remission rates of 77% (95% CI: 70–84%), with relapse rates of 20% (95% CI: 13–27%). The proportion of women achieving a live birth is only 20% (95% CI: 15–25%), despite fertility preservation being a main aim of treatment.

Analysis by treatment type suggests that hysteroscopic resection with adjuvant progestin therapy results in the highest proportion of patients delivering live births (22%, 95% CI: 7.0–38%) and entering remission (84%, 95% CI: 68–100%), with relatively low rates of relapse (9.3%, 95% CI: 0.0–18%). Oral progestins are associated with similar but slightly lower rates of live birth (19%, 95% CI: 13–25%), and remission (77%, 95% CI: 69–84%), but by far the highest rates of relapse of 28% (95% CI: 17–39%). Intrauterine progestins result in the lowest rates of live births (14%, 95% CI: 4.0–23%) and remission (72%, 95% CI: 50–94%), with the lowest rates of relapse (2.1%, 95% CI: 0.0–5.9%). Reassuringly, regardless of treatment protocol, patients who relapsed were successfully treated with a secondary course of progesterone therapy and/or hysterectomy, with no deaths within the follow-up periods reported.

This comprehensive review provides an update of fertility-preserving management for stage 1a grade 1 EC, with a prospectively registered protocol, and synthesis of primary outcome data with meta-analysis. This builds upon previous reviews, which did not assess remission rate (Guillon *et al.* 2019), live-birth-rate (Fan *et al.* 2018) or comprised case-reports and high grade/stage patients outside usual practice (Lucchini *et al.* 2021). We focused on EC rather than considering EH in combination, to provide relevant data for oncology patients. This study excluded cases of fewer than five cases, reducing publication bias. The use of a random-effects meta-analysis helps account for variability between studies.

We acknowledge several limitations. The quality of this review is limited by the available evidence. Studies were heterogeneous in size, findings and treatment protocols. Most studies are small case series, retrospective and lack blinded assessment, indicating a high risk of bias. Fewer than half of studies had 5-year follow up, which may lead to under-reporting of primary outcomes including relapse and live births. Most studies did not report the number of patients actively trying to conceive, or those actively managed by a reproductive-health team, as recommended. Our inclusion of all women in the denominator may have decreased the percentage of women achieving a live birth; however, we feel this approach is justified given that all women initially desired fertility-preservation, and is relevant to patients considering this approach over standard care. The number of patients in each treatment group substantially differed, with the majority of included patients treated with oral progestins. The lower number in other groups limits the accuracy of findings, and the confidence in making comparisons between treatment groups. The omission of studies describing patients with grade 2 disease (W. Shan *et al.* 2021) can be seen as a study limitation in light of recent ESGO/ESHRE/ESGE guidelines allowing consideration of fertility-preservation in such cases after careful counselling, as discussed later (Rodolakis *et al.* 2023).

Overall summary outcomes are similar to previous systematic reviews, which found that hysteroscopic resection with adjuvant progestin therapy achieved the highest rate of complete remission and pregnancy rates (Gallos *et al.* 2012, Fan *et al.* 2018, Lucchini *et al.* 2021). These results are of major importance to women with EC considering fertility-preserving management. Oral progestins are most commonly given for this indication across Europe, followed by LNG-IUS (La Russa *et al.* 2018), yet they may not be the most effective treatments. Hysteroscopic resection of EC is less commonly performed in the United Kingdom and Europe and was not referenced in BGCS guidelines until this year (Morrison *et al.* 2021). The new ESGO/ESHRE/ESGE guidelines now support the approach of hysteroscopic resection followed by oral/intra-uterine progestins (Rodolakis *et al.* 2023), and so this is likely to become more widespread in the coming years.

Possible explanations for this are that resection of the primary lesion along with adjacent endometrium and 3–4 mm of myometrium ensures adequate removal of tumour, and better evaluation of margins and depth of invasion over hysteroscopic biopsy, which may be particularly important given that there is no hysterectomy specimen (De Marzi *et al.* 2015). Concerns have been raised regarding the seeding of tumour cells into the peritoneum during hysteroscopy, with a recent systematic review finding this to be significant for intrauterine pressures above 80 mmHg (Dong *et al.* 2021). However, there is lack of evidence for this in lower stage disease, and no evidence of peritoneal spread among the case series reviewed.

Another potential complication is the risk of intrauterine adhesions, which may adversely impact surveillance biopsies and embryo implantation. This particularly occurs after resection, which damages the basilar layer of the endometrium across widespread or opposing areas of the cavity (Deans and Abbott 2010). There is limited evidence on the incidence of intra-uterine adhesions following hysteroscopic resection of EC (or EH), although a case series of 23 patients reported no instances of intra-uterine adhesions following EC/EH resection, on follow-up hysteroscopic biopsy for a median 25 months (De Marzi *et al.* 2015).

All patients treated with hysteroscopic resection received adjuvant progestin, and so are not at risk of undertreatment. The question is therefore whether hysteroscopic resection confers additional benefit over oral/intra-uterine progesterone alone, and whether this outweighs potential risks. This question is now amenable to consideration in a prospective, multi-centre, randomised controlled trial. Weight loss rates and use of metformin therapy and treatment adjuncts were not assessed in this study, but both have been found to be associated with response in EC and EH (B.-Y. Yang *et al.* 2020, Barr *et al.* 2021, Chae-Kim *et al.* 2021).

We considered only grade 1 stage 1a EC, as this was included within national guidelines at the time of study design; however, the fertility-sparing management of grade 2 stage 1a disease is now included within ESGO/ESHRE/ESGE guidelines (Rodolakis *et al.* 2023). A systematic review of patients with grade 2 disease found poorer overall rates of complete response (64.3%), relapse (23.8%) and live births (eight live births in 54 patients) (Giampaolino *et al.* 2022). Fertility-sparing management in this context may be appropriate in certain women after very careful counselling; however, evidence is limited, and fertility and long-term oncological outcomes may not be as reassuring as for grade 1 disease.

The role of molecular classification in the fertility-sparing management of EC remains to be fully determined. Patients with Lynch syndrome are more likely to develop EC at an earlier age and therefore may have greater interest in fertility preservation (Dominguez-Valentin *et al.* 2020). However, mismatch-repair deficiency appears to be associated with significantly reduced treatment response (Chung *et al.* 2021), and many gynaecological oncologists exclude patients from non-surgical management for this reason (La Russa *et al.* 2018). Mismatch-repair-deficiency (on immunohistochemistry) does not predict failure to achieve complete response after hysteroscopic resection and progestins, but is a highly specific predictor of recurrence (Raffone *et al.* 2021), and small case series have shown patients with confirmed Lynch syndrome have high rates of recurrence and often fail to achieve pregnancy (Catena *et al.* 2022). Whilst routine screening for Lynch syndrome is now standard-of-care in all EC patients, current

guidelines find insufficient evidence to offer recommendations either for or against the consideration of fertility-preserving management in these patients (Concin *et al.* 2021, Morrison *et al.* 2021, Rodolakis *et al.* 2023). The management of other molecular subtypes within the Cancer Genome Atlas classification is similarly undefined, although p53 abnormal tumours are likely to have a poorer prognosis (Arciuolo *et al.* 2022). Other novel biomarkers such as ESR1, WFDC2 and B-cell lymphoma show early promise in predicting cancer progression and prognosis and may have a future role in patient selection (Travaglino *et al.* 2018, Coll-de la Rubia *et al.* 2020). Future studies should routinely report immunohistochemical/molecular profile to enable better patient stratification and identification of high-risk groups.

Conclusions

This meta-analysis reports the reproductive and oncological outcomes of fertility-sparing treatments of EC, thus enabling optimal counselling for women considering this approach. The quality of available data is generally low, with often inadequate duration of follow-up. These results suggest that hysteroscopic resection followed by progestin therapy may produce superior rates of remission and live birth rates compared to other fertility-sparing management options. Further high-quality prospective multi-centre trials are warranted to determine the optimal treatment regime for these patients.

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Author contributions

MO: study selection, data extraction, risk of bias assessment, statistical analysis, manuscript drafting and revision.
SO: study selection, data extraction, risk of bias assessment, manuscript drafting and revision.
RG: study selection and manuscript revision.
AO: conceptualisation, supervision and manuscript revision.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author, MO, upon reasonable request.

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