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Reproductive and pregnancy outcomes of fertility-sparing treatments for early-stage endometrial cancer or atypical hyperplasia: A systematic review and meta-analysis

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ABSTRACT

Objective: To report the pregnancy outcomes of women with prior endometrial cancer and endometrial hyperplasia managed with fertility-sparing treatments.
Methods: Medline and Embase databases were searched. Inclusion criteria were studies reporting the pregnancy outcomes of women who had undergone fertility-sparing treatments for endometrial hyperplasia or early endometrioid endometrial cancer. Outcomes explored were pregnancy, miscarriage and livebirth rates according to the type of progestin treatment used. Subgroup analyses according to the type of diagnostic follow-up were also performed. Meta-analyses of proportions using a random effects model were used to combine data.
Results: Twenty-nine studies (1036 women) were included, and 82.8% [95% confidence interval (CI) 72.3–91.2] of women achieved complete remission. Pregnancy rates were 56.3% (95% CI 41.6–70.5) with megestrol (MA) or medroxyprogesterone acetate (MPA), 63.1% (95% CI 37.0–85.6) with levonorgestrel-releasing intrauterine device (LNG-IUD), 57.9% (95% CI 37.7–76.8) with MA or MPA and metformin, 59.8% (95% CI 48.3–70.7) with MPA and LNG-IUD, 15.4% (95% CI 4.3–42.2) with gonadotropin-releasing hormone analogue (GnRHa) combined with LNG-IUD or letrozole, and 40.7% (95% CI 24.5–59.3) with LNG-IUD and GnRHa. Miscarriage rates were 17.4% (95% CI 12.2–23.4), 14.3% (95% CI 6.4–24.7), 57.9% (95% CI 37.7–76.8), 26.9% (95% CI 14.6–39.3), 100% (95% CI 34.0–100) and 18.2% (95% CI 5.1–47.7), respectively, and livebirth rates were 68.8% (95% CI 56.0–80.3), 80.8% (95% CI 69.5–90.0), 69.9% (95% CI 56.1–82.0), 25.97 (95% CI 14.6–39.3), 0% (95% CI 0–66.0) and 81.8% (95% CI 52.3–94.8), respectively. Finally, stratifying the analysis considering the endometrial sampling method alone, the pregnancy rate was 68.6% (95% CI 51.2–83.6; 10 studies, $I^2 = 83.5\%$) in women who underwent hysteroscopy and 60.5% (95% CI 53.4–67.5; 13 studies, $I^2 = 39.8\%$) in women managed with dilatation and curettage biopsy; the miscarriage and livebirth rates were 13.2% (95% CI 8.0–19.5; $I^2 = 0\%$) and 81.2% (95% CI 67.4–91.8; $I^2 = 67.3\%$), respectively, for hysteroscopy, and 25.2% (95% CI 17.8–33.3; $I^2 = 15.5\%$) and 67.5% (95% CI 58.8–75.5; $I^2 = 0\%$), respectively, for dilatation and curettage biopsy.
Conclusion: Fertility-sparing treatment in women with endometrial cancer or hyperplasia is associated with an overall good response to therapy, good chance of achieving pregnancy and a good livebirth rate. Diagnostic follow-up with hysteroscopy was associated with a higher pregnancy rate, although this requires confirmation in adequately powered randomized trials.

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Introduction

Endometrial cancer is among the most common gynaecological malignancies in developed countries, with approximately 400,000 new cases and 90,000 deaths per year in a recent series [1]. The majority of endometrial cancers occur in women of postmenopausal age, with only about 7% of cases being diagnosed in women of reproductive age [2,3]. In addition, a large proportion of women are diagnosed with complex atypical hyperplasia, a precancerous condition that can lead to overt cancer.

Currently, hysterectomy represents the gold standard of surgical management in postmenopausal women with endometrial cancer and hyperplasia [4]. However, this approach is not a reasonable option for women who wish to achieve pregnancy. In the last two decades, non-surgical approaches aiming to preserve fertility, so-called 'fertility-sparing management', have been proposed as reasonable and safe techniques in women with either endometrial cancer or hyperplasia who wish to achieve pregnancy [5–9]. Such treatments include oral progestins, intrauterine devices (IUDs) that release progesterone, and gonadotropin-releasing hormone analogue therapy [10–15]. Fertility-sparing management represents a viable choice in selected patients with biopsy-proven endometrial hyperplasia or stage IA non-invasive endometrioid adenocarcinoma correctly staged with vaginal ultrasound and/or magnetic resonance imaging.

In these selected cases, patients should be informed that this option is not the treatment of choice, and that adequate surgery is required when their reproductive desire is satisfied, or in cases of persistence or progression of the disease.

Although associated with an overall good complete response rate [16–22], there are no robust data on pregnancy outcomes in women with prior endometrial cancer or hyperplasia treated with fertility-sparing techniques. The large majority of published studies are affected by small sample sizes, lack of data on pregnancy outcomes, and assessment of mainly oncological outcomes. Furthermore, it remains to be elucidated whether the type of post-treatment diagnostic follow-up (hysteroscopy or dilatation and curettage biopsy) may impact the reproductive and pregnancy outcomes of these women.

The aim of this systematic review was to report pregnancy outcomes of women with prior endometrial cancer and endometrial hyperplasia managed with fertility-sparing treatments according to the type of treatment adopted and the post-treatment follow-up diagnostic modality employed.

Materials and methods

Protocol, information sources and literature search

This review was performed according to an a-priori designed protocol recommended for systematic reviews and *meta*-analyses [23]. Medline and Embase databases were searched electronically in September 2020 utilizing combinations of the relevant medical subject heading terms, key words and word variants for 'early endometrial cancer', 'well-differentiated endometrial cancer', 'atypical endometrial hyperplasia', 'complex endometrial hyperplasia', 'fertility-sparing treatment', 'conservative management' 'and 'fertility-preserving treatment'. The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA guidelines were followed [24–27].

Inclusion criteria, outcome measures, study selection and data collection

Studies reporting the pregnancy outcomes of women undergoing fertility-sparing treatments for endometrial neoplasia were included in this review. Only studies reporting pregnancy outcomes in premenopausal women affected by complex atypical endometrial hyperplasia or early endometrioid endometrial cancer, defined as well or moderately differentiated endometrial cancer (G1–2) with no or < 50% myometrial invasion (IA), treated with fertility-sparing management were included in this review. Studies concerning deep myometrial invasion carcinoma, simple hyperplasia, atypical treatment (i.e. photodynamic therapy) or poorly differentiated endometrial cancer were excluded. In addition, case reports, conference abstracts and case series with fewer than five cases were excluded.

Two authors (SDR, DB) reviewed all abstracts independently. Inconsistencies were discussed by the reviewers, and consensus was reached by discussion with a third author (AL).

Full-text copies of those papers were obtained, and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcomes. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

The outcomes explored were intrauterine pregnancies, miscarriages and livebirths.

The number of women who obtained complete remission and were therefore eligible to achieve pregnancy was used as the denominator in this analysis.

All outcomes were explored in the overall population of women with prior endometrial cancer or hyperplasia managed with fertility-sparing treatment, and according to the type of treatment employed, namely:

- megestrol or medroxyprogesterone acetate alone;
- megestrol or medroxyprogesterone acetate plus metformin;
- levonorgestrel-releasing intrauterine device alone;
- MPA plus levonorgestrel-releasing intrauterine device;
- levonorgestrel-releasing intrauterine device plus gonadotropin-releasing hormone (GnRH) analogue; or
- GnRHa and levonorgestrel-releasing intrauterine device or letrozole.

Finally, this review aimed to assess the explored outcomes according to the type of diagnostic follow-up: hysteroscopic evaluation vs dilatation and curettage biopsy.

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS) for cohort studies. According to NOS, each study is judged on three broad perspectives: selection of the study groups; comparability of the groups; and ascertainment outcome of interest. Assessment of the selection of studies included evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and the demonstration that the outcome of interest was not present at study commencement. Assessment of the comparability of studies included evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, ascertainment of the outcome of interest included evaluation of the type of assessment of the outcome of interest, and the length and adequacy of follow-up. According to NOS, a study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability.

Statistical analysis

For quantification of the incidence of outcomes explored, *meta*-analyses of proportions using a random effects model were used to combine data. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was < 10. In this case, the power of the tests is too low to distinguish chance from real asymmetry. Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. All analyses were performed using StatsDirect software (Altrincham, UK).

Results

Study selection and characteristics

In total, 94 studies were identified. Of these, 54 studies were assessed with respect to their eligibility for inclusion, and 29 studies were included in the systematic review (Table 1 and Fig. 1). These 29 studies included 1036 women (range 5–150) with endometrial cancer or hyperplasia managed with fertility-sparing treatment.

Quality assessment of the included studies was performed using NOS for cohort studies (Table S1, see online supplementary material).

Table 1
General characteristics of the included studies.

Study	Country	Year	Study design	Median age (range) (years)	*n* total	Treatment method	Median follow-up (range) (months)	Type of diagnostic method during follow-up
Mazzon et al. 2010 [28]	Rome, Italy	2001–2007	Prospective	33 (27.7–39)	6	Megestrol	50.5 (21–82)	ISC
Mao et al. 2010 [29]	Zhejian, China	2001–	Retrospective	28 (26–31)	6	Megestrol or medroxyprogesterone acetate	50.5 (32–77)	D&C
Minig et al. 2011 [15]	Milan, Italy	1996–2009	Prospective	24 (22–40)	34	Levonorgestrel-releasing intrauterine device and GnRH analogue	29 (4–102)	Pipelle or D&C
Shirali et al. 2011 [30]	Tehran, Iran	2000–2011	Retrospective	32 (24–42)	16	Megestrol	–	D&C
Ricciardi et al. 2012 [31]	Rome, Italy	2003–2009	Retrospective	30 (25–40)	15	Megestrol or medroxyprogesterone acetate	–	ISC
Cade et al. 2013 [32]	Melbourne, Australia	NS	Retrospective	32 (23–42)	10	Medroxyprogesterone acetateand levonorgestrel-releasing intrauterine device	89 (62–142)	D&C
Kim et al. 2013 [33]	Seoul, Korea	2008–2012	Prospective	34.8 (29–40)	16	Medroxyprogesterone acetateand levonorgestrel-releasing intrauterine device	31.1 (16–50)	D&C
Shobeiri et al. 2013 [34]	Tabriz, Iran	2002–2011	Prospective	30 (24–35)	8	Megestrol	34.57 (11–72)	D&C
Parlakgmus et al. 2013 [35]	Adana, Turkey	2004–2011	Retrospective	35 (28–38)	5	Megestrol	–	D&C
Park et al. 2013 (2) [36]	Seul, Korea	1996–2011	Retrospective	30.9 (27.1–34.7)	141	Megestrol or medroxyprogesterone acetate	66 (14–194)	ISC or D&C
Park et al. 2013 (4) [37]	Seul, Korea	–	Retrospective	31 (22–37)	33	Megestrol ormedroxyprogesterone acetate	62.81 (31–160)	ISC or D&C
Shan et al. 2014 [14]	Shanghai, China	2006–2010	Prospective	30 (18–38)	26	Megestrol	32 (15–66)	D&C
Rossetti et al. 2014 [38]	Bergamo, Italy	2005–2012	Retrospective	30 (27–31)	5	Megestrol	36 (14–52)	ISC
Ohyagi-Hara et al. 2014 [10]	Osaka, Japan	2000–2012	Retrospective	34.2 (22.2–43.9)	27	Medroxyprogesterone acetate	39.2 (3.4–153.8)	D&C
Zhou et al. 2015 [39]	Shanghai, China	2006–2013	Retrospective	30.4 (20–40)	32	Medroxyprogesterone acetate/ megestrol and metformin	32.5 (10–92)	D&C or ISC
De Marzi et al. 2015 [40]	Milan, Italy	2010–2014	Retrospective	36.58 (23–43)	23	Oral megestrol	25 (8–37)	ISC
Wang et al. 2015 [8]	Shanghai, China	2006–2015	Prospective	29.5 (25–34)	6	Megestrol	48.5 (26–91)	D&C
Laurelli et al. 2016 [41]	Naples, Italy	2006–2013	Prospective	35.9 (25–40)	21	Levonorgestrel-releasing intrauterine device	85 (30–114)	ISC
Zhou et al. 2017 [42]	Shanghai, China	2012–2016	Retrospective	30 (21–42)	29	GnRH analogue combined with levonorgestrel-releasing intrauterine device or letrozole	18.7 (5.6–54.9)	D&C
Hwang et al. 2017 [43]	Seoul, Korea	2011–2015	Retrospective	30.4 (25–39)	5	Medroxyprogesterone acetate and levonorgestrel-releasing intrauterine device	44.4 (12–71)	D&C
Falcone et al. 2017 [7]	Naples, Italy	2001–2016	Prospective	36.14 (26–40)	28	Oral megestrol or levonorgestrel-releasing intrauterine device	92 (6–172)	ISC
Wang et al. 2017 [44]	Hangzhou, China	2004–2016	Retrospective	27.3 (25–39)	11	Megestrol or medroxyprogesterone acetate	82.3 (15–152)	ISC
Tamauchi et al. 2017 [45]	Nagoya, Japan	2005–2015	Retrospective	34 (19–45)	39	Medroxyprogesterone acetate	52 (16–128)	D&C
Pal et al. 2017 [46]	Houston, Texas, USA	2003–2013	Retrospective	47.1 (18.5–85.2)	46	Levonorgestrel-releasing intrauterine device	50.4 (3.7–144)	ISC
Giampaolino et al. 2018 [47]	Naples, Italy	2007–2017	Retrospective	35.1 (20–44)	69	Levonorgestrel-releasing intrauterine device	–	ISC
Chae et al. 2019 [48]	Seoul, Korea	2005–2017	Retrospective	37 (28–45)	118	Medroxyprogesterone acetate and levonorgestrel-releasing intrauterine device	11.9 (4–49)	D&C
Mitsuhashi et al. 2019 [49]	Chiba, Japan	2009–2017	Retrospective	35 (26–44)	63	Medroxyprogesterone acetate and metformin	57 (13–115)	D&C
Leonerobertimaggiore et al. 2019 [50]	Genoa, Italy	2004–2017	Retrospective	34.5 (29.5–39.5)	48	Levonorgestrel-releasing intrauterine device	82.6 (35.4–129.8)	ISC
B-Y Yang et al. 2020 [51]	Shanghai, China	2013–2017	Prospective	31.5(18–45)	150	Megestrol or megestrol and metformin	–	D&C or ISC

GnRH, gonadotropin-releasing hormone; ISC, hysteroscopy; D&C, dilatation and curettage.

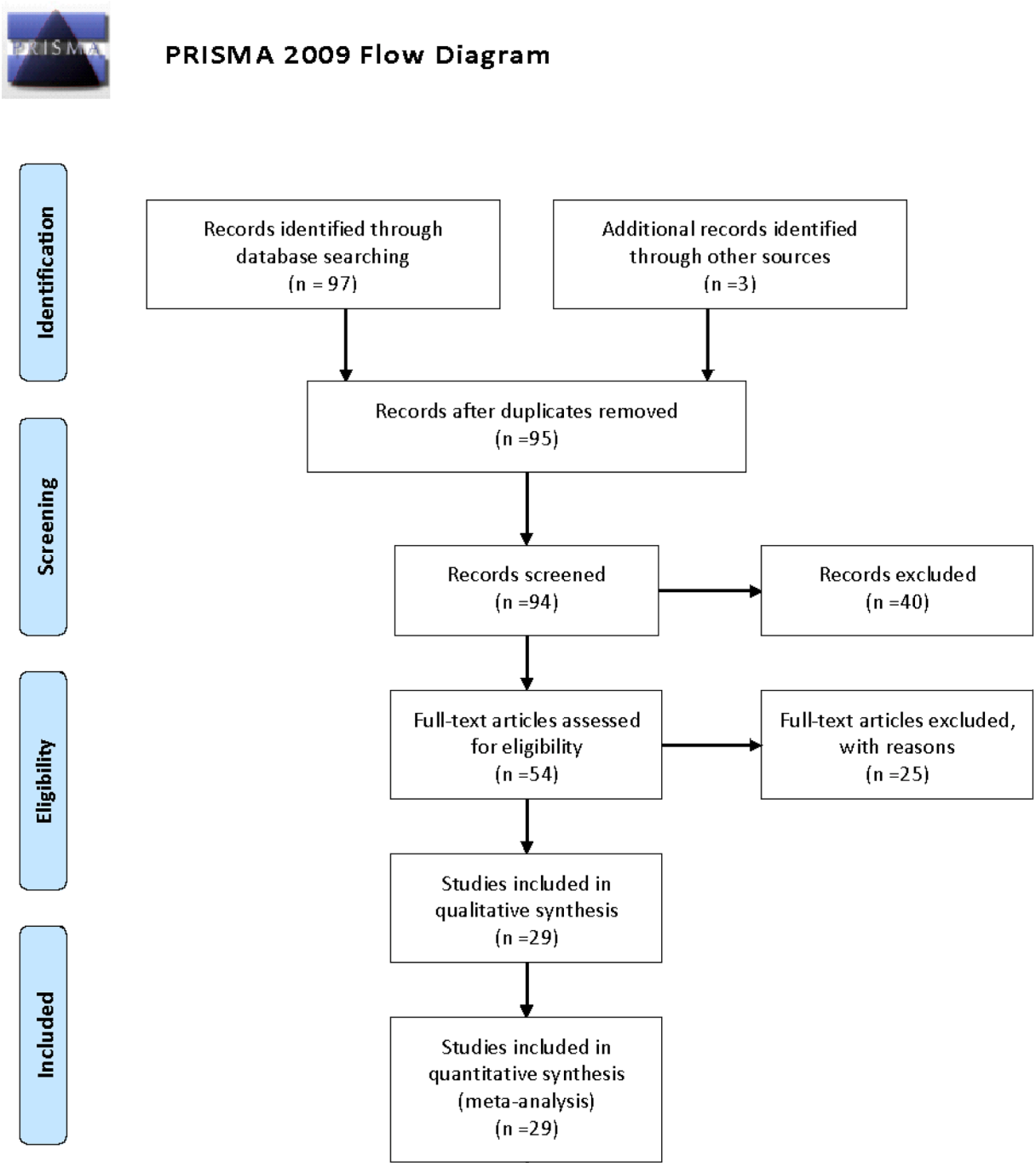

Fig. 1. Systematic review flowchart. From: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6:e1000097. For more information, visit https://www.prisma-statement.org.

Synthesis of the results: Main outcomes

Complete remission of early endometrial cancer or hyperplasia was achieved in 82.8% [95% confidence interval (CI) 72.3–91.2; $I^2 = 93.7\%$] of cases. The number of women who obtained complete remission and attempted to become pregnant was used as the denominator in this analysis. The overall pregnancy rate was 56.1% (95% CI 46.4–65.6; $I^2 = 79.4\%$), the miscarriage rate was 20.6% (95% CI 16.5–24.9; $I^2 = 24\%$), and the livebirth rate was 77.2% (95% CI 72.7–81.5; $I^2 = 25.8\%$).

Table 2 shows the reproductive and pregnancy outcomes of women with prior endometrial cancer or hyperplasia managed with fertility-sparing treatment.

The pregnancy rate was 56.3% (95% CI 41.6–70.5; 17 studies, $I^2 = 81.5\%$) in women treated with megestrol or medroxyprogesterone acetate, 63.1% (95% CI 37.0–85.6; five studies, $I^2 = 82.6$) in women treated with levonorgestrel-releasing intrauterine device, 57.9% (95% CI 37.7–76.8; three studies, $I^2 = 73.7\%$) in women treated with megestrol or medroxyprogesterone acetate and metformin, 59.8% (95% CI 48.3–70.7; four studies, $I^2 = 26.5\%$) in women treated with medroxyprogesterone acetate and levonorgestrel-releasing intrauterine device, 15.4% (95% CI 4.3–42.2; one study) in women treated with GnRH analogue combined with levonorgestrel-releasing intrauterine device or letrozole, and 40.7% (95% CI 24.5–59.3, one study) in women treated with levonorgestrel-releasing intrauterine device and GnRH analogue.

When assessing pregnancy outcomes, the miscarriage rate was 17.4% (95% CI 12.2–23.4; 17 studies, $I^2 = 17.5\%$) in women treated

Table 2
Pooled proportions for the outcomes explored in the present systematic review in women treated with different types of progestin therapy.

Outcome	Studies	Women (*n*/*N*)	Pooled proportions	I^2 (%)
Levonorgestrel-releasing intrauterine device and GnRH analogue				
Miscarriage rate	1	2/11	18.18 (5.1–47.7)	–
Livebirth rate	1	9/11	81.82 (52.3–94.8)	–
Pregnancy rate	1	11/27	40.74 (24.5–59.3)	–
GnRH analogue combined with levonorgestrel-releasing intrauterine device or letrozole				
Miscarriage rate	1	2/2	1 (0.34–1)	–
Livebirth rate	1	0/2	0 (0–0.66)	–
Pregnancy rate	1	2/13	15.38 (4.3–42.2)	–
Medroxyprogesterone acetate and levonorgestrel-releasing intrauterine device				
Miscarriage rate	4	11/45	25.97 (14.6–39.3)	0
Extra-uterine pregnancy rate	4	1/45	6.40 (1.3–15.1)	0
Livebirth rate	4	32/45	69.87 (56.1–82.0)	0
Pregnancy rate	4	42/70	59.77 (48.3–70.7)	26.5
Megestrol or medroxyprogesterone acetate and metformin				
Miscarriage rate	3	16/53	31.19 (19.7–44.0)	0
Livebirth rate	3	37/53	68.81 (56.0–80.3)	0
Pregnancy rate	3	52/89	57.88 (37.7–76.8)	73.7
Megestrol or medroxyprogesterone acetate				
Miscarriage rate	17	29/167	17.42 (12.2–23.4)	17.5
Extra-uterine pregnancy rate	17	4/167	4.26 (1.8–7.7)	0
Livebirth rate	17	136/167	81.03 (74.9–86.5)	21.1
Molar pregnancy rate	17	3/167	2.73 (0.8–5.6)	0
Pregnancy rate	17	158/264	56.29 (41.6–70.5)	81.5
Levonorgestrel-releasing intrauterine device				
Miscarriage rate	5	7/53	14.34 (6.4–24.7)	0
Livebirth rate	5	43/53	80.84 (69.5–90.0)	24.3
Pregnancy rate	5	50/83	63.11 (37–85.6)	82.6

GnRH, gonadotropin-releasing hormone.

with megestrol or medroxyprogesterone acetate, 14.3% (95% CI 6.4–24.7; five studies, $I^2 = 82.6$) in women treated with levonorgestrel-releasing intrauterine device, 57.9% (95% CI 37.7–76.8; three studies, $I^2 = 73.7\%$) in women treated with megestrol or medroxyprogesterone acetate and metformin, 26.9% (95% CI 14.6–39.3; $I^2 = 0\%$) in women treated with medroxyprogesterone acetate and levonorgestrel-releasing intrauterine device, 100% (95% CI 34.0–100; one study) in women treated with GnRH analogue combined with levonorgestrel-releasing intrauterine device or letrozole, and 18.2% (95% CI 5.1–47.7, one study) in women treated with levonorgestrel-releasing intrauterine device and GnRH analogue. The corresponding figures for livebirth rate were 68.8% (95% CI 56.0–80.3; 17 studies, $I^2 = 0\%$), 80.8% (95% CI 69.5–90.0; five studies, $I^2 = 24.3\%$), 69.9% (95% CI 56.1–82.0; four studies, $I^2 = 0\%$), 05 (95% CI 0–66.0; one study) and 81.8% (95% CI 52.3–94.8; one study), respectively.

Subgroup analyses according to endometrial sampling method (hysteroscopy vs dilatation and curettage biopsy)

Table S1 (see online supplementary material) shows all the explored outcomes by type of endometrial sampling method adopted during follow-up (hysteroscopy resection or dilatation and curettage biopsy). In women who underwent follow-up with hysteroscopy, the pregnancy rate was 57.1% (95% CI 40.3–73.2; seven studies, $I^2 = 59.3\%$) in women treated with oral megestrol or medroxyprogesterone acetate and 63.1% (95% CI 37.0–85.6; five studies, $I^2 = 82.6\%$) in women treated with levonorgestrel-releasing intrauterine device, while the corresponding figures for miscarriage were 8.9% (95% CI 2.7–18.2; seven studies, $I^2 = 0\%$) and 14.3% (95% CI 6.4–24.7; five studies, $I^2 = 0\%$) of cases, respectively. Finally, a pregnancy ending with a livebirth occurred in 88.6% (95% CI 78.5–95.8; seven studies, $I^2 = 0\%$) and 88.6% (95% CI 78.5–95.8; five studies, $I^2 = 0\%$) of cases (Table S2, see online supplementary material).

In women undergoing dilatation and curettage biopsy as the endometrial sampling method for follow-up, the pregnancy rate was 54.4% (95% CI 43.4–65.2; eight studies, $I^2 = 35.1\%$) in those treated with megestrol or medroxyprogesterone acetate and 59.8% (95% CI 48.3–70.7; four studies; $I^2 = 26.5\%$) in those treated with medroxyprogesterone acetate and levonorgestrel-releasing intrauterine device, while the corresponding figures for miscarriage were 20.6% (95% CI 10.4–33.2; $I^2 = 29.7\%$) and 26.0% (95% CI 14.6–39.3; $I^2 = 0\%$) (Table S2, see online Supplementary Material).

Finally, when stratifying the analysis considering the endometrial sampling method alone, irrespective of progestin therapeutic protocol, the pregnancy rate was 68.6% (95% CI 51.2–83.6; 10 studies, $I^2 = 83.5\%$) in women undergoing hysteroscopy and 60.5% (95% CI 53.4–67.5; 13 studies, $I^2 = 39.8\%$) in women managed with dilatation and curettage biopsy, while the corresponding figures for miscarriage and livebirth rates were 13.2% (95% CI 8.0–19.5; $I^2 = 0\%$) and 81.2% (95% CI 67.4–91.8; $I^2 = 67.3\%$), respectively, for hysteroscopy, and 25.2% (95% CI 17.8–33.3; $I^2 = 15.5\%$) and 67.5% (95% CI 58.8–75.5; $I^2 = 0\%$), respectively, for dilatation and curettage biopsy (Table 3).

Discussion

Main findings

The findings of this systematic review showed that the overall complete response rate was 83% in women with endometrial cancer or hyperplasia managed with fertility-sparing treatments. Approximately 56% of women subsequently achieved pregnancy, 20% of women experienced miscarriage, and 77.2% of women had a livebirth. When

Table 3
Pooled rates of each pregnancy outcome according to endometrial sampling method.

Outcome	Studies	Women (*n*/*N*)	Pooled proportion	*I*2
Hysteroscopic evaluation				
Pregnancy rate	10	125/206	68.58 (95% CI 51.2–83.6)	83.5%
Miscarriage rate	10	16/128	13.24 (95% CI 8–19.5)	0%
Livebirth rate	10	95/128	81.22 (95% CI 67.4–91.8)	67.3%
Dilatation and curettage				
Pregnancy rate	13	107/176	60.54 (95% CI 53.4–67.5)	39.8%
Miscarriage rate	13	28/113	25.16 (95% CI 17.8–33.3)	15.5%
Livebirth rate	13	77/113	67.46 (95% CI 58.8–75.5)	0%

CI, confidence interval.

stratifying the analysis according to the different types of treatment, megestrol or medroxyprogesterone acetate showed a pregnancy rate of 56%, a miscarriage rate of 17% and a livebirth rate of 81%, while the corresponding figures for levonorgestrel-releasing intrauterine device were 63%, 14% and 80%, although a direct comparison between these two therapeutic approaches could not be performed in a randomized manner.

The pregnancy rate was 57.9% (95% CI 37.7–76.8; three studies, I^2 = 73.7%) in women treated with megestrol or medroxyprogesterone acetate and metformin, 59.8% (95% CI 48.3–70.7; four studies, I^2 = 26.5%) in women treated with medroxyprogesterone acetate and levonorgestrel-releasing intrauterine device, 15.4% (95% CI 4.3–42.2; one study) in women treated with GnRH analogue combined with levonorgestrel-releasing intrauterine device or letrozole, and 40.7% (95% CI 24.5–59.3, one study) in women treated with levonorgestrel-releasing intrauterine device and GnRH analogue.

Finally, when restricting the analysis to the endometrial sampling method alone (hysteroscopy vs curettage), the pregnancy rate was 69% in women who underwent hysteroscopy and 60% in those who underwent curettage. The corresponding figures for miscarriage and livebirth rates were 13% and 25%, and 81% and 67%, respectively.

Strengths and limitations

To the authors' knowledge, this is the first systematic review to assess reproductive and pregnancy outcomes in women with prior endometrial cancer or hyperplasia managed with fertility-sparing treatments. Strengths of this study include its robust methodology for identifying all possible studies for inclusion, assessing data quality and synthesizing all suitable data.

The small number of cases in the majority of included studies, their retrospective non-randomized design, different periods of follow-up, and lack of stratification of the analysis according to maternal characteristics potentially affecting the observed outcomes (e.g. age, body mass index and presence of comorbidities) represent the main limitations of this systematic review. Assessment of potential publication bias was also problematic, both because of the nature of the outcome (rates with the left side limited to the value zero) which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests. The level of evidence for these types of studies is very low. Another limitation is the selection bias in the studies, as the selection of patients was not performed in a controlled or randomized manner in most of the included studies.

Despite these limitations, this review represents the most comprehensive published estimate of reproductive and pregnancy outcomes in women with prior endometrial cancer or hyperplasia managed with fertility-sparing treatments. This is an extremely important issue, as counselling of patients based on small studies that are subject to publication bias may be inadequate.

Implications for clinical practice and research

Hysterectomy may not be an acceptable option for young women with complex atypical hyperplasia or endometrial carcinoma who wish to achieve pregnancy. Fertility-sparing management with progestin is a widely accepted alternative treatment for young women who wish to preserve their fertility [17,52–54]. Women with endometrial-confined, well-differentiated endometrioid adenocarcinoma are candidates for this treatment.

Unfortunately, there is no definitive consensus to date in the published literature on the optimal progestin regimen, duration and follow-up [55].

Moreover, the authors could not perform a direct comparison between oral progestin and levonorgestrel-releasing intrauterine device in view of the lack of such comparison in the original studies, which were also affected by a non-randomized design.

Progestin therapy has an impact on endometrial cells as early as 10 weeks after initiation of treatment, although many authors suggest a minimum of 3 months of treatment before observing a response in the case of endometrial hyperplasia, and even longer in the case of endometrial cancer [45]. Randall and Kurman previously reported that the median length of progestin treatment required for regression is 9 months [56].

The diagnostic method used to evaluate endometrial status during follow-up represents another issue that may affect both oncologic and obstetric outcomes. Classically, follow-up of women with endometrial cancer or hyperplasia is commonly performed using hysteroscopy or dilatation and curettage biopsy.

Hysteroscopic examination of the endometrial cavity allows direct visualization of a suspected lesion, estimation of its extent and complete excision. Conversely, hysteroscopy is considered harmful by some authors as it may lead to a spread of exfoliated endometrial cancer cells into the peritoneal cavity by liquid expansion medium [57,58]. Other authors consider dilatation and curettage biopsy to be the elective diagnostic method in a fertility-sparing setting, because it seems to be associated with the lowest rate of histological undergrading [59–61].

A recent *meta*-analysis reported that hysteroscopic examination before surgery in patients with endometrial cancer was associated with increased risk of dissemination of malignant cells into the peritoneal cavity. This risk was associated with the use of a liquid medium for uterine cavity distention, but not with early-stage disease [62].

More recently, another systematic review exploring prognostic factors for remission in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma [21] reported that operative hysteroscopy for endometrial sampling was associated with higher remission rates, concluding that it should be considered the preferred endometrial sampling method for women with atypical hyperplasia or endometrial cancer undergoing fertility-sparing management.

The type of diagnostic endometrial assessment used may also affect pregnancy outcome, as it can cause injury to the basal layer of the endometrium or underlying myometrium by thermal injury or mechanical destruction [63]. This is crucial as these women commonly require several diagnostic assessments of the endometrial cavity.

In the present systematic review, the pregnancy rate was 69% in women who underwent hysteroscopy and 60% in those who underwent dilatation and curettage biopsy, while the corresponding figures for miscarriage and livebirth rates were 13% vs 25% and 81% vs 67%, respectively. These findings suggest that dilatation and curettage may be more traumatic, causing injury to the basal layer of the endometrium or underlying myometrium, compromising implantation. However, these results should be interpreted with caution as a direct pooled comparison between these two diagnostic techniques could not be performed in view of the lack of such comparison in the original studies, which were also affected by non-randomized designs.

Conclusions

Fertility-sparing treatment in women with prior endometrial cancer or hyperplasia is associated with an overall good response to therapy, good chance of achieving pregnancy and a good livebirth rate. Further large, randomized trials adequately powered for obstetric outcomes are needed in order to elucidate the optimal types of fertility-sparing treatment and post-treatment diagnostic follow-up technique.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2022.04.019.

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