

Review

Fertility-Sparing Management of Early Stage Endometrial Cancer: A Narrative Review of the Literature

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Abstract

Objectives: The incidence of endometrial cancer (EC) is rising largely due to the increasing levels of obesity along with an ageing population. This has led to an increase in the incidence of premenopausal women with EC. 5% of cases are in patients less than 40 years old, 70% of which are nulliparous at diagnosis. Therefore, fertility considerations must be taken into account when managing these patients. The objectives of this review are to present the fertility-sparing management options available. **Mechanism:** A detailed computerized literature search of PubMed and MEDLINE up to 1st June 2022 was carried out in order to survey the evidence for fertility-sparing treatment. Studies including patients with endometrial hyperplasia and early-stage EC undergoing fertility-sparing management were included. **Findings in Brief:** Progestin acts by downregulating oestrogen receptors, thereby suppressing endometrial growth. Oral progestins and the levonorgestrel-releasing intrauterine system (IUS) have therefore been used as non-surgical hormonal treatment for EC. Megestrol acetate (MA) has been shown to produce the highest remission rates compared to other progestins in a systematic review and meta-analysis, but medroxyprogesterone acetate exhibited lower recurrence rates. The IUS for atypical hyperplasia (AH) and EC showed that the majority of patients responded by 3 months' use. A minimum duration of hormonal treatment for AH and EC of 6 months has been advocated, based on randomised studies showing greater efficacy when compared to 3 months treatment. A meta-analysis and systematic review assessing the efficacy of both oral and intra-uterine progestins showed a higher pooled complete response (CR) than with IUS alone. Metformin, gonadotrophin-releasing hormone agonists and weight loss have also been added to progestin regimes with variable results on EC regression. Hysteroscopic resection allows for targeted excision of early-stage EC, but with the risk of perforation and so this has not been recommended by the British Gynaecological Cancer Society or the European Society of Gynaecological Oncology. Assisted reproduction treatment (ART) may be the quickest way to achieve pregnancy once CR is achieved. Pregnancy rates have varied from 32–100%, with live birth rates varying from 17.9–43.8%. **Conclusions:** EC incidence is on the increase in the premenopausal population along with obesity rates and the average first age of parenthood. Fertility-sparing management of EC should be considered for women where fertility is desired.

Keywords: endometrial cancer; fertility-sparing treatment; morbid obesity; fertility conservation

1. Introduction

The incidence of endometrial cancer (EC) is rising largely due to the increasing levels of obesity along with an ageing population [1]. Type I endometrioid carcinoma is driven by oestrogen excess which occurs in obesity due to the peripheral conversion of adipose tissue to oestrogen. This leads to the unopposed stimulation and growth of the endometrium which in turn increases the risk of endometrial hyperplasia and EC. Up to 57% of newly diagnosed cases of EC are due to obesity [2]. This is of enormous concern with obesity levels in Europe projected to increase to 43% by 2025 [3].

EC mainly affects postmenopausal women and the average age at diagnosis is 60 years old [4]. However, the rise in obesity levels has led to an increase in the incidence of premenopausal women with EC. 5% of cases are in patients less than 40 years old [5,6], 70% of which are nulliparous at diagnosis [7]. This coupled with an increase in the av-

erage age of childbearing means that more women will be affected with EC before having started or completed their family. Therefore, fertility considerations must be taken into account when counselling and managing these patients. Letourneau *et al.* [8] surveyed patients after treatment for EC and fertility was reported as one of the most important factors in determining quality of life.

The current gold standard treatment for early-stage EC is hysterectomy and bilateral salpingo-oophorectomy with or without pelvic node dissection. The objectives of this review are to present the fertility-sparing management options available to preserve fertility and assess follow-up and outcomes. A detailed literature search was carried out in order to survey the evidence for fertility-sparing treatment. The results of this search show that complete response to conservative treatment can be achieved in the majority with low rates of disease progression.



2. Indications for Fertility-Sparing Management

Fertility-sparing management of EC can be considered for patients with histologically confirmed grade 1 endometrioid carcinoma without myometrial invasion and the absence of metastatic disease [4]. The most recent European Society of Gynaecological Oncology (ESGO) EC guideline highlights these indications and the possibility of fertility preservation [4]. Current evidence does not support fertility-sparing management of grade 2 or 3 disease without myometrial invasion or stages greater than the International Federation of Gynecology and Obstetrics (FIGO) 1A [4]. Molecular classifications should also be considered. Low risk groups with known molecular classifications for stage I DNA polymerase epsilon exonuclease domain mutations (POLEmut) and mismatch repair deficiency/non-specific molecular profile (MMRd/NSMP) endometrioid carcinoma with negative lymphovascular space invasion (LVSI) indicate good prognosis and could favour a conservative approach [4]. However, intermediate disease of stage 1B or positive LVSI or high grade p53abn cases would not be considered appropriate due to the higher risk of progression and recurrence [4]. The emerging molecular classification of EC will continue to help improve the risk stratification for patients desiring fertility-sparing treatments [2].

Staging investigations should be carried out in the same way as the conventional surgical pathway along with multidisciplinary discussion and decision making. ESGO advises that fertility-sparing management should only be incorporated by experienced gynaecological oncologists with a clear protocol in place, informed consent and strict follow-up measures [4]. Patients must be aware that fertility-sparing management of EC is not the gold standard treatment. They also must be willing to undergo follow-up with regular hysteroscopic surveillance and biopsies, which may not be acceptable to every patient. It is also crucial that patients are counselled to understand that their pre-operative biopsy has its limitations and that hysteroscopic biopsy carries the highest correlation in predicting tumour grade [9]. 3–5% of patients with grade 1, stage 1A disease will have lymph node metastases [10], 5% ovarian involvement [11] or a synchronous ovarian carcinoma in 11–29% [12]. Laparoscopic evaluation has therefore been undertaken in some studies to assess these cases before proceeding with fertility-sparing management [13]. In the event that fertility-sparing management fails, hysterectomy will be offered.

3. Methods

A computerized literature review was conducted from 1950 until 1st June 2022. PubMed and MEDLINE were utilised to identify all relevant studies for patients with early-stage EC or atypical hyperplasia (AH) treated by fertility-sparing means. All applicable studies were appraised along with their references to identify other rele-

vant articles. All studies were assessed by two independent reviewers (MB and AM). Eligibility was initially assessed by consideration of titles and abstracts. Articles were then obtained and the decision to include them was made after comprehensive and meticulous examination. Retrospective cohort studies, case-control studies, prospective studies and randomised control studies were considered for review. The most relevant studies have been reported in order to provide the best available evidence for fertility-sparing management of EC.

4. Studies' Characteristics, Studies' Outcomes

Progestin acts by downregulating oestrogen receptors, thereby suppressing endometrial growth and activating oestrogen metabolism [14]. It also exerts a direct cytotoxic, anti-tumour effect on the endometrium [15]. Oral progestins and the levonorgestrel-releasing intrauterine system (IUS) have therefore been used as non-surgical hormonal treatment for EC. Continuous medroxyprogesterone acetate (MPA) (400–600 mg/day) or megestrol acetate (MA) (160–320 mg/day) are two of the suggested oral progestin regimes with a minimum treatment of 6 months [2].

MA has been shown to produce the highest remission rates compared to other progestins in a systematic review and meta-analysis (odds ratio (OR) 2.70, 95% confidence interval (CI) 1.20–6.02%) [16], but MPA exhibited lower recurrence rates [2]. The bioavailability of MA over MPA is significantly higher and likely accounts for this difference in remission [17]. A meta-analysis of AH and EC by Wei *et al.* [18] showed a pooled complete response (CR) rate of progestin use of 71% (95% CI 63–77%). Zhang *et al.* [19] showed a similar CR rate in EC alone of 79.5% (95% CI 81.7–94.3%) but a recurrence rate of 27.3% (95% CI 18.2–37.6%). These studies have all been incorporated into Table 1 (Ref. [20–37]) to give an overall picture of CR rates.

Yamagami *et al.* [20] addressed the issue of recurrence and repeat treatment in their retrospective series of 162 patients with AH and EC. If after 4 months CR occurred following hysteroscopic visualisation and curettage with MPA treatment, the progestin was then discontinued. If no resolution at this point, 2 monthly sampling was carried out until complete response was achieved. Follow-up was for 2 years with 3–4 monthly biopsies. They were able to demonstrate a CR of 90.7% ($p = 0.097$) in EC patients in the initial treatment group and 98.1% in the repeat treatment arm [20]. 6.2% of EC patients had stable disease with 3.1% progressing [20]. The length of treatment required was similar between the initial and retreatment groups for EC (6.1 versus 6.6 months).

Westin *et al.* [21] conducted a prospective, single-arm trial using IUS for AH and EC with a duration of 12 months. The majority of patients responded by 3 months. The CR rate in EC patients was 66.7% at 12 months, with 4.3% having a partial response (PR), 6.4% stable disease and 10.6%

Table 1. Overview of the reviewed references.

Authors	Study design	No. of patients	Ix	Rx	Median follow-up period	CR Overall (AH/EC)	PD Overall (AH/EC)	Pregnancy rate (AH/EC)	Live birth rate (AH/EC)
Kim <i>et al.</i> [30]	Retrospective	50	AH, EC	Progestin	23 months	35%	-	-	10%
Kim <i>et al.</i> [25]	Prospective	44	EC	MPA + IUS	6 months	37.1%	0%	-	-
Pal <i>et al.</i> [31]	Retrospective	46	AH, EC	IUS	4.2 years	75/67%	6.7/22.2%	-	-
Hwang <i>et al.</i> [32]	Retrospective	5	Grade 2 EC	MPA + IUS	44.4 months	60%	0%	-	-
Maggiore <i>et al.</i> [22]	Retrospective	48	AH, EC	IUS	82.6 months	89.3/81.3%	3.6/12.5%	54.5/100%	17.9/43.8%
Tamauchi <i>et al.</i> [24]	Retrospective	39	AH, EC	MPA	52 months	93/89%	0%	35.9%	25.6%
Yamagami <i>et al.</i> [20]	Retrospective	162	AH, EC	MPA	71.3 months	98.5% 90.7/98.1%	0/3.1%	29.2/22.7%	-
Yang <i>et al.</i> [33]	Retrospective	160	EC	HR + progestin	20 months	97.4%	2.5/2.5%	45%	25%
Tock <i>et al.</i> [34]	Retrospective	16	AH, EC	HR + GnRH	40.7 months	66.7%	0%	53.3%	43.75%
Giampaolino <i>et al.</i> [35]	Retrospective	69	AH, EC	HR + IUS	24 months	92.7/78.6%	0/9.1%	-	40%
Minig <i>et al.</i> [29]	Prospective	34	AH, EC	IUS + GnRH	29 months	95/57.1%	5/28%	32.4%	20.6%
Casadio <i>et al.</i> [36]	Prospective	9	EC	HR + IUS	6 months–5 years	100%	0%	-	-
Park <i>et al.</i> [37]	Retrospective	148	EC	Oral progestin	41 months	77.7%	0%	-	38.3%
Dolapcioglu <i>et al.</i> [23]	Prospective, randomised	104	AH	MPA or IUS	24 months	50% 84%	-	-	-
Westin <i>et al.</i> [21]	Prospective	57	AH, EC	IUS	12 months	83% (90.6/66.7%) 61%	10.6%	-	-
Janda <i>et al.</i> [26]	Prospective, randomised	165	AH, EC	IUS +/- metformin +/- weight loss	6 months	57% 67%	-	-	-
Yang <i>et al.</i> [27]	Prospective, RCT	150	AH, EC	MA +/- metformin	16 weeks & 30 weeks	MA = 20.7% + MF = 34.3%	-	-	-
Mitsuhashi <i>et al.</i> [28]	Prospective	36	AH, EC	MA + metformin	38 months	80.6%	5.6%	-	-

Ix, indication; Rx, treatment; CR, complete response; PD, progressive disease; AH, atypical hyperplasia; EC, endometrial cancer; MPA, medroxyprogesterone acetate; HR, hazard ratio; GnRH, gonadotrophin hormone-releasing hormone; IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate; MF, metformin.

progressive disease amongst both groups [21]. 56.5% reported abnormal bleeding in the first 3 months. Non-responders were less likely to have pathological evidence of exogenous progesterone effect at 3 months ($p = 0.001$) with higher nuclear protein (Ki67) expression ($p = 0.023$) and lower baseline *DKK3* expression ($p = 0.030$) [21]. Quality of life was also assessed with responders reporting significantly higher physical function and vitality scores compared to non-responders ($p = 0.03$, $p = 0.04$ respectively) [21]. There was no difference in body mass index (BMI) between responders and non-responders, but larger median uterine diameter meant non-response was more likely. Maggiore *et al.* [22] conducted a retrospective analysis of the IUS for treatment of EC, with 81.3% CR by 5 months, with CR achieved in 75% of those with grade 2 disease also. Progressive disease was seen in 12.5% of those with grade 1 EC with a relapse rate of 38.5% mostly seen at 25 months post treatment [22].

An IUS is recommended as first line treatment of AH by the Royal College of Obstetricians and Gynaecologists (RCOG) over oral progestins due to its higher disease regression rate, fewer side effects and advantageous bleeding profile compared to oral progestins [38]. This recommendation was based on a meta-analysis and systematic review on patients with simple hyperplasia and showed that the IUS achieved a higher regression rate compared with oral progestins after 3 months (OR 2.30, 95% CI 1.39–3.82%) and up to 24 months of treatment (OR 7.46, 95% CI 2.55–21.78%) [39]. A minimum duration of treatment of 6 months has been advocated, based on randomised studies showing greater efficacy when compared to 3 months treatment [23,38]. Longer term data is lacking, and it is common practice to cease treatment after 6 months with oral agents [38], but 5 years with the IUS is encouraged [20,24,38]. A pooled CR rate for the IUS by Wei *et al.* [18] was 76% (95% CI 67–83%) with a relapse rate of 9% (95% CI 5–17%).

Baker *et al.* [40] conducted a meta-analysis and systematic review assessing the efficacy of both oral and intrauterine progestins in achieving a CR in AH and EC. 219 patients were included with an even split between (complex atypical hyperplasia) CAH and EC [40]. 74% (95% CI 65–81%) of patients with AH and 72% (95% CI 62–80%) of patients with EC achieved a CR with oral progestins compared to 68% (95% CI 45–86%) with intrauterine progestins in EC [40]. Overall relapse was seen in 20.1% of patients after an initial CR [40]. A 2018 meta-analysis of 619 cases showed a CR with oral progestins of 76.3% (95% CI 70.7–81.1%), with a recurrence rate of 30.7% (95% CI 21–42.4%) [41]. The IUS group had a slightly lower CR of 72.9%, (95% CI 60.4–82.5%), with a recurrence rate of 11% (95% CI 5.1–22%) [41]. Both studies noted the lack of high quality evidence and called for prospective randomised control trials [40]. Kim *et al.* [25] conducted a multicentre prospective study to assess the efficacy of the IUS combined with MPA in EC patients. The CR was 37.1% at 6 months with par-

tial response (PR) in 25.7%. No progression was noted. 20.5% of patients withdrew from the study. Wei *et al.* [18] showed a pooled CR of 87% (95% CI 75–93%) when both progestin and IUS are used with Zhang *et al.* [19] showing a higher pooled CR of 94.2% with IUS alone (95% CI 83.2–99.6%) and recurrence of 3.9% (95% CI 0.1–13%), which was significantly lower than with oral progestins alone ($p = 0.0001$).

Side effects and adverse outcomes of progestins are rarely reported in this group of patients. It is crucial in counselling to warn of these possible effects, particularly as the progestin doses are higher than conventional therapy for other benign treatments. Yamagami *et al.* [20] were one of the few papers to report adverse outcomes and side effects. These included weight gain, venous thromboembolism, liver dysfunction and allergic reaction. This represented less than 4% of cases [20].

The recent feMMe trial was a randomised control trial (RCT) of patients with either AH or EC and BMI of greater than 30 kg/m² [26]. Patients were all given the IUS and were randomised to; IUS alone, a weight loss program or metformin 500 mg twice daily [26]. Metformin has antiproliferative activity on endometrial cells which can counter malignant cell proliferation, but it also demonstrates a synergistic effect with progesterone and its inhibitory impact on endometrial growth [26,42]. Weight loss has been shown to improve overall survival in EC patients [43]. The primary outcome was the rate of CR after 6 months. This was achieved in 61% with IUS alone, 67% for those with weight loss and 57% for those with metformin. Overall, the CR for EC alone without AH patients was 43% [26]. The highest rates of progression were seen in the metformin group at 17% [26]. BMI was not predictive of response in this trial. Yang *et al.* [27] also assessed the use of metformin when combined with MA in an RCT versus MA alone for fertility sparing treatment of AH and EC. They assessed CR in both groups at 16 weeks and 30 weeks, finding that CR was achieved in 34.3% versus 20.7%, (OR 2.0, 95% CI 0.89–4.51%, $p = 0.09$) in the MA plus metformin group at 16 weeks, although significance was not achieved [27]. Metformin had a significant effect even in the non-obese group; CR of 51.4% versus 24.3%, (95% CI 1.22–8.84%, $p = 0.02$). No difference was seen in the 2 groups at the 30 week mark [27]. Median weight gain was less in the MA plus metformin group, 2.5 kg versus 5 kg ($p = 0.01$). A similar trial looking at MPA and metformin for EC showed a CR of 81% with a 10% recurrence rate [28].

Chu *et al.* [44] conducted a systematic review of the use of metformin to help prevent and treat EC. Metformin was not associated with a lower risk of EC, but it did significantly improve the overall survival of patients with EC compared to those not taking metformin (hazard ratio (HR) = 0.61, 95% CI 0.48–0.77%, $p < 0.05$), along with reducing the risk of recurrence (OR 0.50, 95% CI 0.28–0.92%, $p < 0.05$) [44]. Its use also improved overall survival of

EC patients with diabetes (HR 0.47, 95% CI 0.33–0.67%, $p < 0.05$) [44]. The review is limited though by the lack of dose or duration of treatment and did not account for statins or aspirin as possible confounders. Chae *et al.* [42] conducted a systematic review and meta-analysis on the outcomes for patients treated with progestin and metformin versus progestin alone for AH and EC. Relapse rates were lower for progestin and metformin than progestin treatment alone (OR 0.46, $p = 0.03$) [42]. The remission rates were not different between the two groups (OR 1.35, 95% CI 0.91–2.00%, $p = 0.14$) [42].

Zhang *et al.* [19] have shown promising results with the use of gonadotrophin hormone-releasing hormone (GnRH) agonists and aromatase inhibitors in fertility sparing treatment for EC patients. As well as the overexpression of oestrogen and progesterone receptors in EC, GnRH receptors are also overexpressed. Minig *et al.* [29] prospectively examined the use of the IUS for 1 year with a GnRH analogue for 6 months. Only 14 patients with EC were included with a complete response in 57.1% and progression in 28% [29].

Obesity is a major risk factor for EC and therefore weight loss advice and planning should be an essential part of any fertility-sparing protocol. 90% of gynaecological patients have expressed the acceptability of discussing weight loss and 50% accepted referral to bariatric services [45]. Evidence of weight loss and recurrence risk after conservative management is lacking. A 2018 Cochrane review analysed the effect of interventions for weight reduction in improving survival in women with EC, but found evidence was limited and of low quality [43]. Combined behaviour and lifestyle interventions did not improve overall survival (relative risk (RR) 0.23, 95% CI 0.01–4.55%, $p = 0.34$), nor were they associated with significant weight loss (mean difference -1.88 kg, 95% CI -5.98 – 2.21 kg, $p = 0.37$) [43].

The impact of bariatric surgery in EC patients is also deficient. Fast track access to a bariatric service for consideration of weight loss surgery should be offered to all patients in line with NICE guidance if they have a BMI of over 50 kg/m^2 [46]. Obese women who lose 5% or more in weight have been shown to reduce their EC risk by 56% [47], therefore RCTs are needed to assess the impact in EC patients to assess whether an expediated service would improve oncological outcomes.

Hysteroscopic resection allows for targeted excision of early-stage EC, along with a more detailed evaluation of margin status and molecular classification than can be gained from dilatation and curettage (D&C) alone [2]. However, there is risk of perforation in pursuing hysteroscopic resection and this treatment has not been recommended by British gynaecological cancer society (BGCS) or ESGO. Hysteroscopic resection has been carried out prior to commencement of progestin treatment, but case series remain small and complications not always recorded.

Giampaolino *et al.* [35] carried out a series of 69 patients with both AH and EC treated with hysteroscopic resection followed by IUS insertion. Only 14 of these had EC [35]. 78.6% in the malignant group had CR with 18.2% having a subsequent relapse after 24 month follow-up and 9.1% having progression [35]. Yang *et al.* [33] conducted a retrospective study and analysed 40 patients with EC managed with hysteroscopic resection of suspected lesions. Progestin therapy was started after hysteroscopic evaluation with MA 160 mg/day, 50% were also on metformin as part of their cancer treatment [33]. CR was seen in 97.3% of patients at 18 months follow-up, with mean treatment to achieve CR seen at 6.4 ± 0.6 months [33]. Factors favouring a quicker complete response were BMI $< 25 \text{ kg/m}^2$ and lesion size $\leq 2 \text{ cm}$ [33]. No serious adverse event of hysteroscopic resection occurred in this group. Masciullo *et al.* [48] were also able to demonstrate that with hysteroscopic resection followed by oral progestin treatment, shorter treatment durations were needed to achieve a CR, along with longer times to relapse when compared to progestin treatment alone. No adverse events were reported. A meta-analysis by Zhang *et al.* [19] showed a pooled CR rate following hysteroscopic resection and oral progestin treatment of 98.1% compared to progestins alone of 77.2%, $p < 0.0001$ in AH and EC patients combined with a recurrence rate of 4.8%. A study by Marzi *et al.* [49] found no intrauterine adhesions on follow-up hysteroscopy after fertility-sparing hysteroscopic resection.

Tock *et al.* [34] carried out a retrospective study of 8 patients with EC, assessing the combination of endometrial resection followed by a GnRH agonist with a 3 month follow-up interval. 57% had CR at 3 months with 43% having stable disease [34]. No patients had relapse or progression after a median follow-up of 40.7 months. No intrauterine adhesions occurred but no adverse hysteroscopic events were recorded.

Endometrial ablation is not advised as an alternative treatment for EC as complete destruction cannot be guaranteed, disease may persist and surveillance can be made challenging with intrauterine adhesions [38].

5. Fertility Outcomes

The RCOG advises that there must be at least one negative endometrial biopsy before trying to conceive with AH, but referral to a fertility specialist should be sought before attempting to conceive [38]. European society of human reproduction and embryology (ESHRE) has produced a guideline on female fertility preservation, acknowledging fertility loss as a detrimental impact of cancer treatment [50]. Assisted reproduction treatment (ART) may be the quickest way to achieve pregnancy whilst also reducing the time frame before definitive surgery can be carried out. ART also minimizes the window of unopposed oestrogen stimulation of the endometrium whilst aiming to ensure the shortest time in which relapse or disease progression could occur.

Yang *et al.* [27] showed a pregnancy rate of 37.5% for their patients undergoing fertility-sparing treatment of EC. A live birth rate of 25% was reported in those actively trying to conceive, but this was a mixture of both AH and EC patients [42]. Maggiore *et al.* [22] showed a pregnancy rate of 100% in those with EC, 75% of which underwent *in vitro* fertilisation (IVF) with a live birth rate of 43.8%. Wei *et al.*'s [18] meta-analysis of AH and EC showed a pooled pregnancy rate of 34% (95% CI 30–38%) after progestin treatment, with a 20% live birth rate. Zhang *et al.*'s [19] live birth rate for EC patients alone was higher at 32.3% (95% CI 22.9–42.5%).

In Giampaolino's [35] series, 40% that had their IUS removed following hysteroscopic resection achieved a live birth after natural conception in the 12 months of follow-up. Wei *et al.*'s [18] meta-analysis of IUS treatment showed a pooled pregnancy rate of 18% (95% CI 7–37%) with a live birth rate of 14%. When the IUS and progestin treatment was undertaken, pooled pregnancy rate increased to 40% (95% CI 20–63%) with a 35% live birth rate [18]. Fan *et al.*'s [41] meta-analysis highlighted a pregnancy rate of 52.1%, 95% CI 41.2–66% with oral progestins, 56% (95% CI 37.3–73.1%) after treatment with the IUS and 47.8% (95% CI 37.3–73.1%) after hysteroscopic resection and progestin therapy.

Chae *et al.* [42] also looked at pregnancy outcomes after fertility-sparing management for AH and EC after CR. Progestin and metformin compared to progestin only achieved similar, non-significant pregnancy and live birth rates. 54% became pregnant in the combined treatment group versus 48% in the progestin only portion [42]. 66.6% of these patients achieved a full term birth, 3.3% preterm birth and 23.3% miscarriages [42]. The median time from end of treatment to successful pregnancy was 7.67 months [42]. Only 1 pregnancy out of 30 resulted from natural conception, the rest required ART of varying degrees. The only multivariate analysis that was shown to have an effect on predicting pregnancy failure was grade of disease (OR 6.2, 95% CI 1–38.9%, $p < 0.005$) [42]. Yamagami *et al.* [20] showed a pregnancy rate of 20.8% after initial treatment, with 22.7% after retreatment. Yang *et al.*'s [27] RCT of MA plus metformin versus MA alone showed a pregnancy rate of 51.8% and 48.4% respectively, $p = 0.8$.

It is important to note that despite CR with conservative treatment, young obese EC patients will still face the challenges of fertility and obstetric outcomes that are associated with the metabolic syndrome of obesity. Adverse outcomes of those with obesity include increased rates of pregnancy induced hypertension, pre-eclampsia and gestational diabetes. Prepregnancy counselling by a medical obstetric team should also be conducted so patients are aware of these added risks.

6. Follow-Up

Assessing response to fertility-sparing treatment is needed along with ensuring progression of disease has not occurred. ESGO guidelines advise that hysteroscopic visualisation and biopsy along with repeat imaging must be carried out at 3–4 and 6 months [4]. If no response at 6 months is seen, standard surgical management should then be recommended [4]. Continuous hormonal treatment should be used until pregnancy is desired. Six-monthly follow-up is then advised with transvaginal ultrasound (TVUSS) and physical examination [4]. Hysteroscopic and endometrial biopsy are only advised if TVUSS indicates abnormal findings or there is abnormal uterine bleeding. Hysterectomy and bilateral salpingo-oophorectomy is recommended as soon as childbearing is complete due to the risk of recurrence and progression. The RCOG greentop guideline recommends fertility-sparing surveillance of AH be managed with 3-monthly biopsies until two consecutive negative samples, and then 6–12 monthly biopsies [38]. A flowchart of suggested management is presented below in Fig. 1.

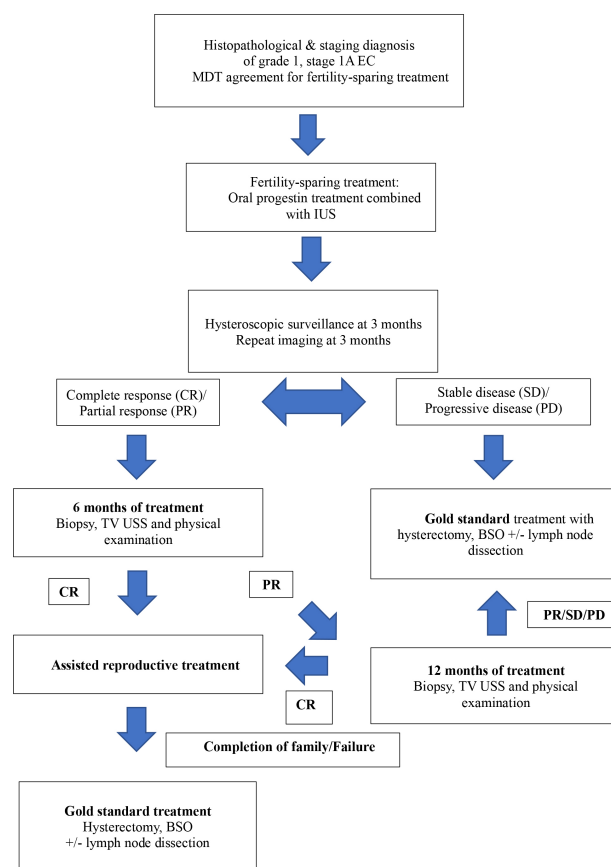


Fig. 1. Flowchart of management of fertility-sparing treatment of EC.

7. Prognosis

It is crucial that patients undergoing fertility-sparing treatment are given the best available evidence of the risk of relapse and progression of cancer. Disease progression whilst on oral progestins was reported as 2.7% in a meta-analysis and systematic review by Baker *et al.* [40], whilst another review highlighted 33.1% went on to have a hysterectomy for various reasons and myometrial invasion was found in 14.8% of those cases [16]. Remission probability plateaus at 12 months and recurrence probability increases continually for at least 5 years [16]. Koskas *et al.* [16] looked at recurrence and could find not factors which led to an increased likelihood of the event. They showed that the recurrence probability increased with longer length of time, the 4-, 6-, 12-, 18- and 24- month recurrence probabilities were 3.6%, 9.6%, 17.2%, 26% and 29.2% respectively [16].

Progestin and metformin treatment combined have lower disease relapse than progestin alone [42]. However combined therapy was not associated with different remission rates, pregnancy or live birth rates [42]. Other progestin regimes compared to MA were associated with an increased probability of progression, OR 3.95, 95% CI 1.44–10.81% [16]. The relapse rate after hysteroscopic resection from Yang *et al.*'s [33] series was 11.1% seen at a median of 7 months. Only 1 patient out of 40 showed progression to superficial myometrial invasion confirmed on histology after hysterectomy [33].

Patients at higher risk of relapse with AH are those with BMI >35 kg/m² [38]. Two long-term prospective studies have shown only 3% patients relapse when their BMI is <35 kg/m², but 33% when >35 (HR 5.51, 95% CI 1.05–28.87%) [38]. Park *et al.* [37] showed that the BMI threshold for failure of complete regression was in fact lower when the BMI was ≥25 kg/m² (OR 2.14; 95% CI 1.06–4.31%, $p = 0.033$), in a patient population less than 40 years of age.

Pregnancy has been shown to slow the rate of recurrence of endometrial cancer after complete remission. Median disease free survival was shown by Chae *et al.* [42] to be 26 months in those that had a pregnancy, compared to 12 months in the non-pregnant group ($p < 0.005$).

Overall survival after fertility-sparing treatment of EC at the 2-, 5- and 10-year mark were all 99% respectively for EC after initial treatment, with 100% respectively amongst the retreatment group in Yamagami *et al.*'s [20] analysis. Greenwald *et al.* [51] assessed a cohort of 161 (2.5%) women whom initially received hormonal therapy for grade 1 and 2, stage 1 EC and followed them up for a median of 6.9 years in comparison to those that received standard surgery (6178 patients, 97.5%) to assess long-term survival. All-cause mortality was not significantly different between the groups, 14.1% in the hormone group versus 9.3% who underwent surgery [51]. Cancer-specific mortality was non-significantly higher in the hormone therapy group of 9.2% versus 2.1% in the surgery group. This difference was ac-

counted for by 3 late deaths in the hormone cohort, and remained non-significantly higher when grade 1 EC only was examined; 10 yr mortality of 15.67% versus 7.83% in the conventional treatment group [51]. BMI or parity were not collected and could account for the differences [51]. Therefore, the use of hormone therapy as an alternative to standard surgical treatment does not appear to affect long-term survival albeit with the limitations of these studies, more studies are needed to assess survival in this cohort of patients. A centralized database of these patients receiving fertility preserving treatment is required to give more accurate survival data, as advocated by the Gynecological Inter-Group [52].

8. Strengths and Limitations

This review has been able to incorporate all the relevant studies in a field not widely explored in gynaecological oncology with few randomised control trials. This review has been able to also appraise the more recent randomised feMMe trial which highlights the important contribution of weight loss as an adjunct to tackling EC in fertility-sparing management. This review is limited by the fact that there are few randomised studies assessing the fertility-sparing approach and other studies have low patient numbers, but highlights the need for more robust evidence in this area, particularly as this is going to become an increasing problem in line with the escalating obesity rates amongst this patient population.

This review can help shape an evidence-based fertility-sparing management protocol in clinical practice. The importance of a weight loss programme with access to bariatric services should be part of a holistic approach in conjunction with an expedited referral to fertility services. A progestin used in combination with metformin should be considered to lower relapse rates. MA has been shown to have higher remission rates yet MPA shows less recurrence. The IUS is also effective but without the same progestin side effect profile, so treatment can be tailored to individual patients and their morbidities.

9. Conclusions

EC incidence is on the increase in the premenopausal population along with obesity rates and the average first age of parenthood. Fertility-sparing management of EC has not traditionally been considered a feasible option for women. However, due to changing patient demographics, it is imperative that these options be discussed with patients where fertility is desired and that they are managed through a specialist gynae-oncology multi-disciplinary team (MDT). The use of weight loss as an adjunct to treatment with progestins should be part of the overall management along with the concurrent use of metformin to lower relapse rates. The choice of progestin needs to be individualised taking in to consideration patients' wishes and tolerance of oral progestins.

Author Contributions

AM conducted the literature review and wrote the manuscript. JC/MB supervised, read, and approved the final manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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