Best Practice & Research Clinical Obstetrics and Gynaecology 55 (2019) 93–108

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

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

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Challenges and controversies in the conservative management of uterine and ovarian cancer

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Keywords:
Uterine neoplasms
Ovarian neoplasms
Conservative treatment
Surgical procedures
Women's health

A B S T R A C T

Uterine cancer is the fifth most common cancer in women worldwide with an estimated 320,000 annual diagnoses. Its most common form, endometrioid adenocarcinoma of the endometrium (endometrial adenocarcinoma [EAC]), is thought to develop through excessive proliferation of endometrial glands, and then increasing steadily in incidence. The current standard treatment for EAC is hysterectomy, which is often curative. However, it may be unacceptably expensive for women with severe medical comorbidities, those who are at risk of intra- and postoperative adverse events and those who desire fertility.

Ovarian cancer is the most malignant of all gynaecological cancers, but patients with disease limited to one ovary and patients with non-epithelial tumours may expect a good prognosis. A selected group of young patients who desire fertility may be well treated with conservative surgery.

This chapter reviews patient selection, diagnosis, pre-treatment evaluation, treatment options, surveillance and risk of relapse.

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https://doi.org/10.1016/j.bpobgyn.2018.08.004
1521-6934/

Endometrial cancer

Introduction

Endometrial cancer is the most common gynaecological malignancy in many countries in the world and the fifth or sixth most common cancer overall among females. Worldwide, in 2012, it has been estimated that 320,000 women are diagnosed with endometrial cancer [1]. Its incidence and burden is increasing steadily, for example, in the USA from 49,560 in 2013 to 61,380 in 2017. In Australia, women currently already have a 2.5% lifetime risk of developing endometrial cancer. Survival outcomes with current standard treatment, which consists of hysterectomy and bilateral salpingectomy, are excellent (above 80% in 5 year survival), especially for women diagnosed with low-grade endometrial adenocarcinomas (EACs). However, comorbidities may have an impact on survival outcomes [2]. In the past, nonsurgical treatment was used on a case-by-case basis for young women who had a desire for fertility. Increasingly, non-surgical treatment may also be required for women who have a high comorbidity burden.

Endometrial carcinomas considered for nonsurgical treatment

Broadly, two types of endometrial cancer are distinguished: Type 1 endometrial cancer includes low-grade tumours of the endometrioid cell type [3], whereas Type 2 endometrial cancer is not thought to be associated with obesity. With improvements in molecular biology and genetic diagnostics, finer subgroupings may be considered for their value to guide clinical decision making in the future [4] [5].

Type 1 EAC (85%) typically presents with well-differentiated tumours, with no or minimal invasion into the surrounding myometrium, and carries a good prognosis. This means that it is usually not aggressive and slow to spread into lymph nodes or neighbouring tissues. The main risk factor for Type 1 EAC is obesity [6–8]. EAC is commonly diagnosed at early stages because postmenopausal or irregular bleeding is an early warning sign or women are investigated for infertility, thus triggering investigations and early treatment. Hormonal nonsurgical treatment may be considered for women with this subtype.

Type 2 endometrial cancer (15%) is not associated with obesity, and patients with these tumour types are ineligible for conservative hormonal treatment, which will not be discussed here [3].

Risk factors for EAC: One key reason for the increase in EAC incidence is obesity. Obesity is characterised by an abundance of fat cells, which produce oestrogens through various biological pathways and stimulate abnormal metabolism in the endometrium, which is highly sensitive to oestrogens. Endometrial hyperplasia, hyperplasia with atypia, and EACs are all thought to be consequences of this dysregulation, virtually always resulting from chronic oestrogen oversupply unopposed by the counterbalancing effects of progesterone. Currently, three main pathways by which obesity is thought to lead to EAC are considered:

Hormonal signalling

The endometrium is exquisitely sensitive to steroid hormones that act through well-known nuclear receptors. Oestrogen stimulates epithelial proliferation predominantly through the oestrogen receptor ERα, whereas progesterone inhibits growth and causes cell differentiation through progesterone receptors (PRs). Expression of PRs is common in endometrioid cancers. Most risk factors for Type 1 EAC relate to oestrogen pathways, although the exact mechanisms are still not understood (summaries of potential pathways [6,7,9,10]); thus, an anti-oestrogenic, progesterone-based approach for the treatment of EAC has been advocated for many years with some success.

Inflammation

Obesity is also associated with chronic low-grade inflammation that is attributed to increased levels of circulating pro-inflammatory cytokines [11]. Non-steroidal anti-inflammatory drugs have recently been shown to reduce breast cancer recurrence and extend disease-free survival by at least 2 years in overweight and obese women [12], thus suggesting that inflammatory mediators may promote

tumourigenesis in obese individuals [13]. Data indicate that many cytokines are present in the adipose tissue and some are secreted at elevated levels in obese females. Cytokines such as IL-6 and TNFα are, on average, expressed twofold and fourfold higher in obese females, respectively, than in normal females. Both cytokines have previously been implicated in mouse models of obesity-related inflammation and carcinogenesis [14], and their expression is reported to decrease with weight loss (reviewed by Ref. [15]).

PTEN-PI3K-AKT-mTOR pathway

Although the importance of oestrogen-controlled pathways has been highlighted, there are other stimuli that modulate cell growth in the EAC setting. Phosphatidylinositol 3-kinase (PI3K) pathway aberrations occur in >80% of Type 1 EAC, with the dominant activating event being loss of PTEN protein expression [16]. Absence of functional PTEN protein leads to unopposed action of PI3K with resultant uncontrolled activation of the AKT and mTOR pathways. Activation of these pathways can lead to dysregulation of hormonal signalling. Functional loss of PTEN can result from a variety of genomic and epigenetic defects [16] and is believed to be an early event in endometrial carcinogenesis [17], being observed in up to 83% of endometrioid cancers and 55% of pre-cancerous lesions [18].

Precursor lesions of EAC: Excessive proliferation of cells in the glands located within the endometrium, referred to as **Endometrial Hyperplasia** may show cytological atypia (endometrial hyperplasia with atypia [EHA]), which may progress to or coexist with EAC [19]. It virtually always results from chronic oestrogen stimulation unopposed by the counterbalancing effects of progesterone.

EHA (the thickening of the lining of the uterus due to excessive proliferation of cells in the glands) is seen as a pre-cancerous condition of EAC [20–22]. Indeed, invasive EAC is found on final histopathology in 20–40% of patients who already had a hysterectomy for assumed EHA [19,23] (Fig. 1).

The key risk factor for endometrial hyperplasia, namely, obesity, is same as that for EAC. In most countries, EHA is not a notifiable disease; therefore, data of its incidence are not available. A Brazilian study that investigated endometrial biopsies on 193 non-symptomatic overweight or obese women (mean BMI: 35 ± 7 kg/m^2) found EAC and EHA in 1.5% and 0.75% of biopsies, respectively [24].

Diagnosis of EAC, EHA or hyperplasia without atypia

To achieve a diagnosis of EAC, the endometrial tissue is to be obtained through a formal *Dilatation and Curettage* (D&C) and submitted for pathological assessment, with sufficient tissue volume for reliable diagnosis being very important. Alternatively, endometrial sampling in an outpatient setting may be used and has been found to be extremely reliable [25]. The likelihood of EAC upon hysterectomy is only 0.9% if a previous endometrial sampling had a negative result. The process of endometrial sampling may cause temporary cramp pain (comparable to that occurring in a menstrual period), which subsides after completion of the procedure, and slight vaginal bleeding/spotting for 1–2 days. The risks of repeated D&Cs (day surgical procedure) are minimal. Uterine perforation is uncommon (0.3% in premenopausal and 2.6% in postmenopausal patients) [26]; other complications are rare.

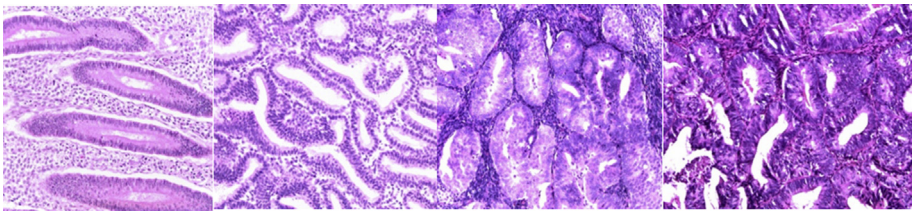

Fig. 1. (From left to right): Normal, proliferative endometrium; Complex hyperplasia without atypia; Endometrial Hyperplasia with Atypia (EHA); Endometrial Adenocarcinoma (grade 1).

Diagnostic imaging

The purpose of imaging is to confirm that the tumour originates from the endometrium and to confirm the extent of the disease. Most clinicians would agree that for any consideration of conservative treatment, the tumour should not invade deeper than one half of the myometrium and will not involve retroperitoneal nodes or extrauterine sites, in which case conservative treatment would clearly be insufficient for tumour control.

The absence of extrauterine disease is typically confirmed on a CT scan of the pelvis, abdomen and chest. The role of pelvic MRI to determine the depth of invasion has been described in detail [27]. The negative predictive value of MRI to exclude deep myometrial invasion is higher than 95%.

Tumour markers

Serum CA125 is a blood tumour marker commonly used in the context of ovarian malignancy. In the context of endometrial cancer, we evaluated the role of CA125 to exclude extrauterine disease. Preoperative CA125 level, but not other preoperative clinical characteristics, was found to be associated with extra-uterine spread of disease. Utilizing a cut-off point of 30 U/ml achieved a sensitivity, specificity, positive predictive value and negative predictive value of 31.0%, 88.5%, 36.7% and 85.7%, respectively [28]. An elevated CA125 level above 30 U/ml in patients with apparent early-stage disease is a risk factor for the presence of extra-uterine disease and may assist clinicians in the management of patients with clinical stage I EAC.

In another work, we have shown that CA125 and HE4 levels were higher in stage III and IV tumours ($p < 0.001$) and in tumours with outer-half myometrial invasion ($p < 0.001$) [29]. Area under the curve analysis demonstrated that HE4 was a better predictor of outer-half myometrial invasion than CA125, particularly in patients with low-grade endometrioid tumours (AUC 0.77 vs 0.64 for CA125). These data highlight the possible utility of HE4 for pre-operative risk stratification to identify high-risk patients within patients with low-grade EAC who might not qualify as candidates of conservative treatment.

Standard treatment of EAC

The current standard treatment for both EHA and EAC is total hysterectomy and bilateral salpingo-oophorectomy with or without surgical staging. Prognosis of Type 1 EAC is generally excellent (recurrence-free survival [RFS] is >90% at 5 years), and 50% of all deaths are due to underlying medical comorbidities (e.g. obesity, hypertension and diabetes) rather than the EAC itself [30]. Although radical surgery offers excellent survival outcomes, it also has undesirable consequences: slow recovery from surgery, surgical adverse events, loss of fertility and financial and societal treatment costs [31,32].

Consequences of EAC treatment by surgery: The development of EHA or EAC is problematic not only for young premenopausal women who still wish to have children, but may lose their uterus if treated by surgery, but also for women who may be not be suitable for surgical treatment.

The *Gynaecologic Cancer InterGroup* identified non-surgical treatment for women at high risk of adverse events or for those who still desire children as one of the **most pressing research priorities in endometrial cancer.** [33,34] Similarly, *The James Lind and Womb Cancer Alliance Priority Setting Partnership* identified further studies on the impact of lifestyle changes including weight loss for EAC as one of the **top 10 research priorities.** [23] The *American College of Obstetricians and Gynaecologists* described the challenge currently faced by women and their treating clinicians: "… while non-surgical treatment may be considered for the treatment of EAC in women who want to have more children or women who cannot have surgery because of other medical reasons, women must decide to undertake such treatment recognising that **information about future outcomes is limited"**.

Treatment of EAC by progestational agents: Conservative hormonal treatment has been used for many years in young patients who desire to have children. Data are available from many studies that describe treatment success for women with hyperplasia with or without atypia, but much less data are available for women with EAC. There are a few case series including a

retrospective report by Cade and Quinn on 16 cases [35]. Systematic reviews or meta-analyses attempted to summarise outcomes; however, most available studies used multiple oral progestational treatments, were case reports or case series only, did not use a randomised design and differed in the treatment prescription and study endpoints. There was also inconsistent data on follow-up, with data missing for many of the reviewed studies [36–38]. The use of oral progestins in this setting is problematic. The main side effects of oral progestins include thrombo-embolic complications (DVT, PE and stroke), weight gain (through fluid retention) and the onset or worsening of diabetes mellitus (Type 2). Currently, systemic (oral) progestins are mainly used for the treatment of endometrial cancer recurrence and in palliative care. Oral progestins are not established for the treatment of primary EAC owing to concerns of side effects (diabetes, thromboembolic events, peripheral oedema and weight gain) and low patient compliance, and there are many variations in the formulation (medroxyprogesterone, megestrol acetate, hydroxyprogesterone caprotate and unspecified progestin formulations), dosage, length of treatment and combination with other agents. By contrast, intrauterine progestin is not known to cause systemic side effects, and the intrauterine device (IUD) releases 52 mg of levonorgestrel (LNG) at a consistent rate of 20 μg/24 h and declines to 10 μg/24 h after 5 years. Adherence is much easier with the IUD than with oral medications, which are often taken at less than ideal frequency by many patients [39].

Only one multicentre randomised trial was conducted for women with EHA only, and the patients were assigned to either LNG-IUD, continuous (daily) or cyclical (10 days per cycle) medroxyprogesterone (10 mg). Response rates were 100%, 96% and 69% for these groups, respectively [40].

Gunderson et al. reviewed 45 studies, which reported on 280 women with EAC and 111 with EHA who received one or more progestational agents; 80% of the patients were administered with agents delivered orally, whereas 20% of them received an IUD. Women with EHA had better response to treatment than women with EAC, but the authors did not report on whether oral or IUD treatment was more successful maybe because some women received a combination of both.

Baker et al. conducted a meta-analysis focussing on high-quality studies only. For inclusion, studies had to report on at least 10 or more eligible patients with EHA or EAC in either the oral or IUD treatment arm; patients had to receive 6 or more months of treatment and should not have received other treatments. The review found only 12 such studies and reported that oral and IUD treatments were similarly effective, although evidence was much more limited for IUD-delivered progestins. In patients with stage 1 EAC treated with intrauterine progestins, the mean pathological complete response rate was 68% (95% CI 45–86%) compared to 72% (95% CI 62–80%) using oral hormonal treatment.

Recent results and pregnancy outcomes

Pal et al. reviewed 46 patients treated with LNG-IUD and found similar response rates of 75–80% among women treated for EAC and EHA [41]. Interestingly, women with a larger uterus size and those with a lack of exogenous progesterone effect in the pathology were found to have a lower likelihood to respond.

Previous studies reported that the average time to response was 6 months. In patients with endometrial hyperplasia, a meta-analysis by Gallos reported a pregnancy rate of 75/325 with some women achieving more than one birth. Recently, Minig and colleagues administered LNG-IUD in women for 1 year, plus a GnRH analogue for 6 months. Overall, 19/20 (95%) patients with EHA and 8/14 (57.1%) patients with EAC responded, whereas one (5%) and four (28%) patients with these diagnoses, respectively, recurred after a follow-up of 36 months. Eleven spontaneous pregnancies occurred in 9/34 women [42]. In another non-randomised study including 70 young women, 23/32 (72%) patients with EAC and 35/38 (92%) of patients with EHA responded, and 8/53 women who tried to conceive succeeded with 10 healthy births [43]. These results and those of other studies show that effective pregnancy outcomes can be achieved among young women who select progestational treatment owing to the desire to have children [43].

Although previous studies did not find a reduced response rate to progestin among obese women, obesity may have an impact on the fertility rate among patients successfully treated with progestin for EAC [44]. Lifestyle changes to reduce comorbidity burden are therefore critical for young women who desire to regain fertility. There is a lack of data from randomised trials on whether combining LNG-IUD with other treatments, e.g. antidiabetic drugs, weight loss or dietary changes, may increase response or fertility outcomes. [43],[28] Women are motivated to embrace lifestyle change after a cancer diagnosis, yet definitive guidelines for EAC cancer survivors are yet to be developed. Evidence published by the World Cancer Fund suggests an increased risk of EAC with a high dietary glycaemic index and a low risk of EAC with high coffee intake. There is evidence that overall diet quality might be an important prognostic risk factor for several cancers. [29] The important role of glycaemia and insulinaemia in cancer progression has led to dietary interventions testing the feasibility of carbohydrate restriction among EAC cancer survivors (NCT0328515), but studies using lifestyle interventions in combination with progestational agents as conservative treatment for EHA and EAC are lacking.

Hysteroscopic resection

Resection of the EHA or EAC by hysteroscopic techniques alone or in combination with progestational agents has been reported in a small number of case reports or case series. In 2006, Sparac and colleagues first used the combination treatment for a woman with Lynch syndrome, followed by Vilos and colleagues in 2007, again reporting on an individual case. Mazzon combined hysteroscopic resection of grade 1 EAC with 160 mg/day megestrol acetate treatment, whereas Laurelly combined hysteroscopy with either oral or intrauterine progesterone, both studies achieved complete response in all but two of the combined 20 patients. This result was similar to that of a study by Shan and colleagues, who reported a complete response in 21/26 patients after the combination hysteroscopic treatment followed by progestin treatment. Alonsos reviewed the combined literature showing an excellent response in 32/36 patients, with recurrence in 11% of patients only.

Radiation treatment

Radiation treatment is an inappropriate choice for women who wish to retain fertility but may be an appropriate alternative to surgery for patients with EAC who are medically unfit for surgery. It can consist of external beam radiation treatment (45–50 Gy) with or without intracavitary brachytherapy [45,46]. Local control rates of 75%–80% have been reported and depend on the FIGO grade of differentiation.

We must consider that the vast majority of patients selected for radiation treatment are medically impaired and their prognosis would be significantly compromised by their underlying medical condition. Hence, for most patients, palliation and prevention of complications from either the disease or the treatment is the primary objective, rather than long-term survival.

Recurrence

Given the wide range of response rates reported, recurrences of EHA or EAC after conservative treatment are common [47,48]. A meta-analysis [49] suggested that approximately 40% of patients treated conservatively will recur. For example, in a retrospective study, response to treatment in women with EHA or EAC was similar to that in women receiving oral, IUD-delivered or combination treatments, with about a third of patients having persistent disease and 13% of them were found to have disease upon hysterectomy [50]. Given that with hormonal treatment the underlying risk factors leading to EAC in the first instance remain present and unchanged and given that the initial treatment may be discontinued, especially if women wish to conceive, this will not be surprising.

In case of localised recurrence, second-line treatment with topical or systemic progestins has shown promising response rates. In a small case series of three patients, aromatase inhibitors have been added to the progestin treatment, with successful outcomes [51].

Surveillance

The recent ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer guidelines indicate that recurrence rates are high in patients who completed conservative treatments [52]. They recommend follow-up every 6 months. Patients who have bleeding need to be investigated as need be. Their risk of a relapse is particularly high.

After fertility is completed, consideration should be given to a completion hysterectomy.

Given that studies consistently found non-response or recurrence when using hormonal treatment alone, the search for a new agent and combination treatments is intensifying.

Window of opportunity trials

A number of window of opportunity trials are currently underway, which studies the value of interventions before hysterectomy. Most trials are non-randomised, and their endpoint is biologic response.

Some trials combine progestational agents with those that are designed to impact the mammalian target of rapamycin (mTor) pathways such as everolimus or metformin. Everolimus belongs to the family of signal transduction inhibitors. Signal transduction inhibitors restrain signals within cells that make them grow and divide. It is already used in lung, pancreatic and gastrointestinal cancers, but its impact on EAC needs further investigation. Its side effects are similar to those resulting from the use of other transduction inhibitors and include mouth sores, immunosuppression, fevers, chills and skin rashes. The antidiabetic drug metformin inhibits mTOR through the activation of upstream adenosine monophosphate (AMP)-activated protein kinase (AMPK) [53] and is associated with reversal of resistance to progestins [16]. Evidence for metformin as a medication effective against EAC comes from in vitro [16,53], pharmaco-epidemiological [54] and window of opportunity studies [55,56]. Soliman and colleagues enrolled 20 patients with EAC, who received metformin 850 mg p/o daily for $\geq$7 days. Significant serum and molecular marker improvements were observed from before to after surgery [56]. Metformin is usually very well tolerated; side effects of diarrhoea, nausea and liver and kidney function suppression are fairly uncommon and well manageable by dose reductions.

Current, on-going clinical trials

At the time of writing this manuscript, no randomised controlled clinical trial that would inform us about the effectiveness of conservative treatment options in endometrial cancer is completed.

Starting in 2008, the first nonrandomised clinical trial was conducted. The feMMe trial was the first randomised controlled trial (RCT) in this area, and its results are expected to become available in 2020. Since then, a number of RCTs have been initiated. An overview of clinical trials is provided in Table 1.

Ovarian cancer

Epithelial ovarian cancer is predominantly a disease of postmenopausal women, with an average age at diagnosis of 63 years. In Australia, approximately 7% of ovarian cancer cases are diagnosed in women aged below 40 years [57]. Twenty-five per cent of them are diagnosed at stage 1, with the remaining 75% diagnosed at stage 2 or greater; 53% are stage 3–4 at the time of diagnosis.

Optimal surgical treatment for ovarian cancer requires surgical staging and, if advanced, cytoreduction. The standard staging procedure includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, pelvic and para-aortic lymph node dissection and omentectomy. Assessment of the upper abdomen and peritoneal surface biopsies are also required [58].

Fertility-sparing surgery (FSS) is widely accepted in malignant germ cell tumours, which most commonly affect younger women [59]. It is also accepted in the management of borderline epithelial ovarian tumours [60]. Attempts to preserve fertility by performing less radical surgery may also be an option for younger women presenting with localised epithelial ovarian cancer, and this has been investigated in numerous studies.

Table 1
Summary of current clinical trials of conservative treatments.

Title	Clinicaltrials.gov ID	Commencement Date	Institution	Population/Eligibility	Intervention/Outcome
Levonorgestrel Intrauterine Device (IUD) to Treat Complex Atypical Hyperplasia (CAH) and Grade 1 Endometrioid Endometrial Carcinoma (G1EEC)	NCT00788671	2008	M.D. Anderson Cancer Center	50 participants aged ≥18 years old with a diagnosis of complex atypical grade 1 endometrioid endometrial carcinoma	Levonorgestrel IUD Complete Regression of Disease at 1 year
Treatment With Medroxyprogesterone Acetate Plus LNG-IUS in Young Women With Early Stage Endometrial Cancer	NCT01594879	2012	Korean Gynecologic Oncology Group	39 patients aged <40 years old with biopsy-proven grade 1 endometrioid adenocarcinoma that is presumably confined to the endometrium	LNG-IUS insertion while taking oral MPA 500 mg/day Response rate at 24 months
Metformin With the Levonorgestrel-Releasing Intrauterine Device for the Treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients	NCT02035787	2014	UNC Lineberger Comprehensive Cancer Center	30 women aged ≥18 years old with histologically confirmed CAH or grade 1 EC	Metformin (850 mg BD) added to treatment with levonorgestrel-Releasing Intrauterine Device Response rate at 6 months
Phase II Study of Intrauterine Device (IUD) Alone or in Combination With Everolimus in Endometrial Cancer	NCT02397083	2015	M.D. Anderson Cancer Center	270 women aged ≥18 years old with a diagnosis of complex atypical hyperplasia OR grade 1 endometrioid endometrial carcinoma on endometrial biopsy or D&C within 3 months of study enrolment	Levonorgestrel IUD vs Levonorgestrel IUD + Everolimus 10 mg/day Response rate at 6 months
Mirena® ± Metformin as Fertility-preserving Treatment for Young Asian Women With Early Endometrial Cancer	NCT02990728	2016	Chang Gung Memorial Hospital, Taiwan	120 women aged ≤40 years old with histologically confirmed grade 1 endometrioid adenocarcinoma of the endometrium	Mirena vs Mirena + metformin (unknown dose) Efficacy of about 6 months
Megestrol Acetate Plus LNG-IUS in Young Women With Early Endometrial Cancer	NCT03241914	2017	Fudan University	40 women aged 18–45 years old with a diagnosis of endometrioid endometrial cancer	Megestrol acetate 160 mg/day vs MA (160 mg po qd) plus LNG-IUS Pathological response rate

					up to 12 months Pathological response time up to 12 months
An Endometrial Cancer Study for Women With Recurrent or Persistent Endometrial Cancer	NCT03077698	2017	Xenetic Biosciences, Inc.	70 women aged ≥18 years with serous carcinoma or endometrioid type of endometrial carcinoma who have recurrent or persistent progressive disease that is refractory to curative therapy or established treatments and cannot be treated with surgery or radiotherapy	Sodium cridanimod and progestin therapy (megestrol acetate) combination Tumour assessment up to 52 weeks
Value of LNG-IUS as Fertility-preserving Treatment of EAH and EC	NCT03463252	2018	West China Second University Hospital	224 women aged ≤40 years old with a strong desire for fertility preservation and histologically confirmed EAH or grade 1 EC	MPA (250 mg-500 mg qd) only vs MPA (250 mg-500 mg qd) + LNG-IUS vs LNG-IUS only Pathologic response at 6–9 months Pregnancy Rate at 7–15 months Live Birth Rate at 16–24 months

This paper reviews FSS in ovarian cancer. Recommendations from society guidelines are reviewed, along with publications related to FSS, minimally invasive compared to open surgical approach for FSS, the role of adjuvant chemotherapy and obstetric outcomes.

Fertility-sparing surgery – society recommendations

The 2017 National Comprehensive Cancer Network guidelines [61] suggest that FSS may be adequate for selected patients. Tumours included in this recommendation are stage 1A and 1C tumours and/or low-risk (grade 1) tumours. Comprehensive surgical staging is recommended for these patients, including unilateral salpingo-oophorectomy, omentectomy, peritoneal lavage, peritoneal biopsies and cytology, and para-aortic plus pelvic lymphadenectomy.

The European Society for Medical Oncology guideline [6] has a similar stance; however, it makes a recommendation that mucinous, serous, endometrioid or mixed histology be considered for fertility preservation. The importance of comprehensive staging is again emphasised, including performing lymphadenectomy (although the recommended extent of lymphadenectomy is not stated).

Earlier recommendations from the European Society of Gynaecological Oncology [62] recommended FSS only in patients with stage 1A, grade 1 serous, mucinous or endometrioid tumours, with consideration of FSS in stage 1A grade 2 and stage 1C grade 1 disease. Adequate staging is again considered as mandatory.

Biopsy of the contralateral ovary, if normal in appearance, is unnecessary. The risk of microscopic metastases to the contralateral ovary appearing as normal was 2.5% in a series of fully staged patients with disease apparently contained to one ovary [63]. Counselling such patients with regard to the risk of occult persisting disease is therefore of vital importance.

Fertility-sparing surgery – studies

Numerous retrospective cohort studies have recorded the outcomes of FSS in early epithelial ovarian cancer. A 2016 systematic review considered 39 articles describing 1150 patients undergoing FSS [64]. The overall recurrence for stage 1 disease (across all grades and histological types) was 11%, with 10% in stage 1A disease and 16% in stage 1C disease.

Further breakdown of stage and grade demonstrates an expected increase in recurrence, with increasing stage and grade of disease; 7% stage 1A grade 1, 11% stage 1A grade 2 and 29% stage 1 grade 3. Similarly, recurrence increased from 11% stage 1C grade 1, 11% stage 1C grade 2 and 23% stage 1C grade 3 disease. The use of adjuvant chemotherapy was not considered in this publication, as the focus was on the surgical aspect of care for these patients.

Of note, the comprehensiveness of surgical staging was not consistent across the studies included in this systematic review. At the most basic level, this was considered at least unilateral salpingo-oophorectomy with omentectomy, through to pelvic/para-aortic lymph node sampling with multiple peritoneal biopsies, subtotal omentectomy and washings. Given that previous evidence has suggested that up to 30% of apparent early-stage ovarian cancer will be upstaged after comprehensive surgical staging [65,66], it is likely that a proportion of women included in these studies would have had inadequate staging, and therefore, their oncological outcomes could be compromised.

Fifty-one of 1092 patients (including upstaged patients) included in this review undergoing FSS died due to disease, with a follow-up of between 20 and 132 months; data on overall survival (OS) were not available. This equates to a disease-specific survival rate of 95%.

Outcomes of FSS compared to those from radical surgery have been considered in several retrospective publications, with no significant difference in disease-free survival or OS between the two groups [67–70].

Laparoscopy compared to laparotomy

Laparoscopic surgery has become increasingly prevalent. A Cochrane review found no RCTs or appropriately designed studies to help ascertain the role of laparoscopy for the management of early-stage ovarian cancers [71].

A recently published systematic review [72] pooled results from 11 retrospective publications, with a total of 3065 patients. There were no statistically significant differences in operating time, blood loss or length of hospital stay, although there was a trend in favour of patients undergoing laparoscopy. There were less post-operative complications in patients undergoing laparoscopy; however, incidence of severe complications was similar in both groups.

Cyst rupture and nodal yield are concerns in the laparoscopic approach; this systematic review found similar results between both groups. Importantly, pooled data did not demonstrate any difference in survival or recurrence outcomes.

Adjuvant chemotherapy

The role of adjuvant chemotherapy in early-stage ovarian cancer has been assessed in two RCTs, both published in 2003. Neither of these specifically considered FSS.

The ICON1 study [73] analysed the outcomes of 447 women with early-stage epithelial ovarian cancer, where the responsible clinician was uncertain whether immediate chemotherapy was indicated. Women were randomly assigned to either adjuvant chemotherapy immediately after surgery (n = 241) or no adjuvant chemotherapy until clinically indicated (n = 236). The extent of surgical staging was not described, with the only surgical criteria being that all visible tumour had to be removed; thorough surgical staging with total hysterectomy and bilateral salpingo-oophorectomy, where appropriate, and omentectomy was recommended as the minimum procedures. Chemotherapy regimen was recommended to be either single-agent carboplatin or cyclophosphamide, doxorubicin and cisplatin combination treatment, at three-weekly intervals for six cycles; other platinum-based combination treatments were also allowed.

ICON1 demonstrated a benefit in OS and progression-free survival in favour of adjuvant chemotherapy (5 year OS 79% vs 70%, RFS 73% vs 62%). It must be recognised that approximately 16% of the patients included in analysis were FIGO stage II or III; in addition, the extent of staging was not clear. Both these factors could have a negative impact on these figures.

The ACTION study [74] was run parallel to the ICON1 study and evaluated the outcomes of 448 women with early-stage ovarian cancer who were randomised to either receive adjuvant platinum-based chemotherapy (n = 224) or observation after surgery (n = 224). Extent of staging was analysed; comprehensive staging was strongly advised, however, performed in only 34%. Chemotherapy regimen was at least four cycles of platinum-based regimen, with a recommendation for six cycles.

A RFS benefit was again seen in the chemotherapy arm (76% vs 68%); however, there was no statistically significant OS benefit (85% vs 78%). Further analysis according to the extent of staging demonstrated no benefit with chemotherapy in the optimally staged patients; however, in patients who were not optimally staged, there were statistically significant improvements in PFS and OS with adjuvant chemotherapy. Of note, FSS was considered appropriate for inclusion.

A Cochrane review [75] published in 2016 considered the role of adjuvant chemotherapy for early-stage ovarian cancer. Four RCTs were of sufficient quality for inclusion, with 95% of participants having stage 1 epithelial ovarian cancer. Adjuvant chemotherapy was associated with improved OS and progression-free survival at both 5 and 10 years. Subgroup analysis was unable to confirm or refute survival benefit in those with a lower risk or optimally staged disease.

Fertility outcomes

Several studies described the number of patients attempting, and achieving, pregnancy after FSS [76–79]. Collectively, 158 women attempted to conceive, with 121 women attaining pregnancy (76.5%). There were 148 live births. For those publications that recorded the presence or absence of congenital abnormalities, there were no congenital abnormalities amongst 21 women with live births who had received adjuvant platinum-based chemotherapy.

Practice points

Ovarian Cancer

- Fertility-sparing surgery for early-stage epithelial ovarian cancer appears to be a reasonable option, although the retrospective nature of all the data (except for adjuvant chemotherapy) is a clear limitation. Recurrence and survival rates appear to be acceptable.
- A laparoscopic approach is not of proven benefit; however, the differences between this and a traditional open approach seem to be in favour of the laparoscopic group. It remains unclear whether future randomised data will help give further direction on this topic despite a widespread trend towards minimally invasive approaches.
- Adjuvant chemotherapy has an established role in oncological outcomes after surgery for early-stage epithelial ovarian cancer.
- Fertility outcomes appear to be favourable, with no reported congenital abnormalities amongst women receiving adjuvant chemotherapy, although this is limited by small numbers.

Uterine Cancer

The review has shared evidence on the conservative treatment of endometrial cancer. Although progress has been made during the last few years, important questions remain unanswered:

- Efficacy of treatment: Whether proposed better treatments are indeed effective is to be confirmed through clinical RCTs or meta-analysis of multiple RCTs. Results of RCTs in conservative treatment of EAC are still missing but will be available shortly.
- Prediction of response: From multiple retrospective analyses, we anticipate an overall response rate of 50%–80%. However, and even more importantly, the challenge will be to identify factors predictive of response or nonresponse.
- The patient perspective: There is a risk of nonresponse that may cause anxiety and uncertainty. Conservative treatment also has the inconvenience of multiple minor surgical procedures, as each follow-up examination requires assessment of a uterine biopsy to ascertain the absence of disease. In addition, patients often present with their own or their family's preference, knowledge and attitudes. Current evidence does not provide good guidance on how women perceive those challenges and how these women can be counselled. Previous studies have mostly been retrospective and little information beyond medical details has been collected [49,80]. None reported in-depth data on women's experience of fertility-sparing surgery or active surveillance.
- Follow-up intervals and duration: Most studies reported regular follow-up using D&C or endometrial sampling every 3–6 months, with change in progestational agent or dosage or standard treatment hysterectomy offered to patients who experience a recurrence. However, the American College of Obstetricians and Gynaecologists describes the challenge for women and their treating clinicians: "while non-surgical treatment may be considered for the treatment of EAC in women who want to have more children or women who cannot have surgery because of other medical reasons, women must decide to undertake such treatment recognising that information about future outcomes is limited" [81]. Concerns that women need to consider when making an informed decision include the risk of recurrence, which current evidence estimates at approximately 30%; there is a need for stringent follow-up procedures.

Research agenda

- The need for the development of conservative treatments in EAC is generally and widely accepted [82].
- Various treatment options are available and are currently tested.
- Most treatments focus on obesity-associated, Type 1 EAC (low-grade, superficially invasive endometrioid adenocarcinoma of the endometrium).
- High-quality data from RCTs on the efficacy of conservative treatments in EAC are not available as yet.
- Evidence on predictive factors will be crucial to identify candidates for RCTs.
- The patient perspective of conservative treatments in EAC needs to be studied and understood to maximise the benefits of these treatments.
- Increasingly combination chemotherapy and immunotherapy is being considered for ovarian cancer. The impact of these new combinations on fertility-sparing surgery outcomes needs to be assesses.

Conflicts of interest

None to declare.

Funding

MJ is funded through a NHMRC Translating Research into Practice Fellowship (App1151021).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bpobgyn.2018.08.004.

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