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Endometrial cancer

Vivek Arora, MBBS, MD, Dip NB (India), MRCOG (UK), FRANZCOG, Fellow Gynaecological Oncology [a,*], Michael A. Quinn, MB ChB, MGO, MRCP (UK), FRANZCOG, FRCOG, CGO, Professor [a,b]

[a] Royal Women's Hospital, Parkville, Victoria 3052, Australia
[b] University of Melbourne, Melbourne, Victoria, Australia

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Endometrial carcinoma is the most common gynaecological malignancy in the Western world. The standard management of endometrial carcinoma is total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymph-node dissection. Increasingly, endometrial cancer is being diagnosed in younger women in whom preserving fertility may be an important consideration when deciding optimal management. Conservative management of endometrial carcinoma may be a therapeutic option in carefully selected women with well-differentiated endometrial cancer in the absence of any myometrial invasion or adnexal disease seen on imaging. The biggest concern with conservative management of endometrial carcinoma is disease progression while on treatment or after initial response to medical treatment. Women opting for conservative management should be aware that hormonal therapy is not the standard form of management. Potential adverse outcomes should be taken into consideration.

Introduction

Endometrial carcinoma is the most common gynaecological malignancy in the Western world. The lifetime risk of developing endometrial cancer in the USA is estimated to be as high as 2.6%.[1] The peak incidence of endometrial cancer is in the early sixth decade. Differing reports on the proportion of women diagnosed with endometrial carcinoma under the age of 45 years (5–30%) probably reflect the

* Corresponding author.
E-mail address: vbbarora@yahoo.com (V. Arora).

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difference in the referral patterns of the institutions from where the data are published.[2] Undoubtedly, endometrial cancer is being diagnosed increasingly in younger women in whom preserving fertility may be an important consideration when deciding optimal management (Fig. 1). In the recent Surveillance, Epidemiology, and End Results statistics, 1.6% of all endometrial cancers were diagnosed between the ages of 20 and 34 years and 6.1% between the ages of 35 and 44 years.[1] Most of these are type 1 or hormone-dependent cancers associated with endometrial hyperplasia.

Endometrial cancer tends to be diagnosed at an early stage in most women, and is usually associated with a good prognosis. The 5-year survival for disease confined to the uterus is as high as 96%.[1] The standard management of endometrial carcinoma is total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymph-node dissection.

Risk factors

Obesity, nulliparity and a history of polycystic ovarian syndrome are known risk factors for the development of endometrial carcinoma. More importantly, the incidence of these risk factors is higher in women aged 40 years or younger.[3] All these conditions are associated with unopposed oestrogenic stimulation of the endometrium. The risk of developing endometrial carcinoma increases 10-fold in women weighing 23 kg more than the ideal body weight. Nulliparity is associated with a relative risk of 2.0, whereas co-existent diabetes mellitus has been associated with a relative risk of 2.7, probably caused by increased aromatisation of androgens in this condition.[3]

Genetic predisposition is the other main cause of developing endometrial cancer at a younger age. Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant disorder caused by mutations in a family of DNA mismatch repair genes. Women with HNPCC have a 40–60% risk of

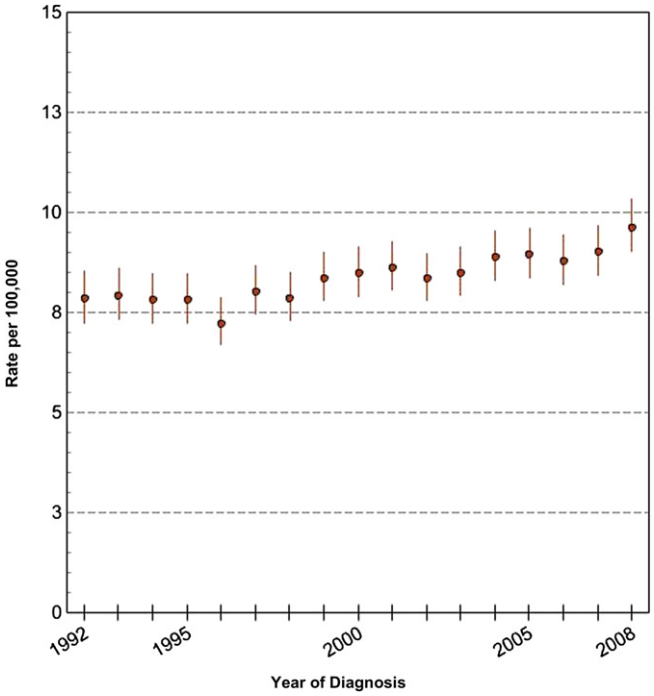

Fig. 1. Increasing incidence of endometrial cancer in young women. *Age-adjusted Surveillance Epidemiology and End Results incidence rates and 95% confidence intervals cancer site: Corpus and uterus, NOS ages 20–49, all races, female years 1992–2008. Cancer sites include invasive cases only unless otherwise noted. Incidence source: SEER 13 areas (San Francisco, Connecticut, Detroit, Hawaii, Lowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monlerey, Los Angeles. Alaska native registry and rural Georgia). Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups census P25-1130).

developing endometrial carcinoma.[4] Conversely, the risk of HNPCC mutation in women diagnosed with endometrial cancer under the age of 50 years is more difficult to define.[5]

Patient characteristics associated with diagnosis of endometrial carcinoma under the age of 45 years

Histology

Endometrioid adenocarcinoma is the predominant type of histological diagnosis in 90% of women diagnosed with endometrial carcinoma. High-grade tumours, including clear-cell carcinoma, papillary serous type carcinoma, mixed type of endometrial carcinoma, and undifferentiated adenocarcinomas are diagnosed in the remainder. These histological types were previously thought to only affect older women.[3] This emphasises the importance of expert pathological review in a tertiary-care service before offering conservative management to women desirous of fertility preservation.

Metastatic and synchronous ovarian malignancy

Bilateral salpingo-oophorectomy is recommended at the time of hysterectomy for endometrial carcinoma because of the risks of ongoing hormonal stimulation of any unrecognised metastatic deposits and because of the risk of synchronous or metastatic ovarian malignancy.

Ovarian metastases have been reported in as many as 5% of women with grade one endometrial carcinoma, and are reported more often in women who fail conservative management.[6] In a population-based review, women diagnosed with endometrial cancer below the age of 45 years were more likely to be diagnosed with a synchronous ovarian malignancy (14% *v* 2%).[7] Other investigators have reported an increased incidence of synchronous and metastatic ovarian tumours in women who either fail to respond to conservative management or experience a recurrence soon after treatment cessation.[8,9] Walsh et al.[10] reported a 25% incidence of synchronous and metastatic ovarian malignancies in women diagnosed with endometrial cancer under the age of 45 years. Two-thirds of these were associated with grade one endometrial tumours and just over one-half were associated with less than 50% myometrial invasion.

In a prospective Gynecologic Oncology Group study, the reported rate of synchronous ovarian malignancy was 5%.[11] Reported rates of synchronous ovarian malignancy in studies of conservative management of endometrial carcinoma range from 7–29%.[3,12] In a study reporting 19% synchronous ovarian tumours, 78% of the ovarian tumours were visible macroscopically at the time of laparoscopy. Another 10% of women had microscopic ovarian cancer detected on histo-pathological examination.[3] In a further prospective observational study that included pre-treatment magnetic resonance imaging (MRI) and diagnostic laparoscopy as part of the work up, 14% of women with presumed early stage endometrial carcinoma were diagnosed with synchronous ovarian malignancies.[13] Several studies, including those mentioned above, have highlighted the fallibility of macroscopic evaluation of ovaries at the time of laparoscopy or definitive surgery in predicting occult malignancy.[3,10,12]

Lymp-node metastasis

Metastatic disease to the lymph nodes is an important consideration before embarking upon conservative management of endometrial carcinoma in young women. Depth of myometrial invasion and grade of endometrial carcinoma are both independent risk factors for lymph-node metastasis. The risk of lymph-node involvement with grade one endometrial carcinoma that is non-invasive is essentially negligible. The seminal paper by Creasman et al.[14] defined the risk factors for lymph-node involvement in endometrial carcinoma based on the older International Federation of Gynecology and Obstetrics staging system, and suggested that there was no risk of lymph-node involvement in a grade one endometrial carcinoma that was limited to the endometrium. The risk increased to 3% with depth of invasion to inner third of myometrium.[14] In a recent single-institution retrospective review, the risk of lymphatic spread was 0% with grade 1 tumours and any depth of myometrial invasion in women with clinical stage 1 disease in whom at least eight lymph nodes had been removed.[15] In view of the

difficulties in assessing depth of invasion on imaging studies, only women with grade one endometrial carcinoma on curettage specimens and no evidence of myometrial invasion on imaging should be considered for conservative management to ensure optimal oncological outcomes.

Prognosis

It has been stated that younger women diagnosed with endometrial carcinoma tend to have favourable disease characteristics, including lower grade and stage at presentation, which translates into a favourable prognosis.[16–18] In a population-based study, it was suggested that younger women are more likely to be diagnosed with a lower grade endometrial carcinoma. Early stage at diagnosis in most of these women is thought to be associated with a better prognosis.[19] Conflicting evidence, however, suggests otherwise.[2] In a cross-sectional review, a higher proportion of younger women (less than 45 years) were diagnosed with lower-grade disease limited to the endometrium; however, the distribution across stages I–IV was similar to those diagnosed with endometrial carcinoma at over 45 years of age. More women under the age of 45 years were diagnosed with synchronous ovarian malignancies than the other group. It was also suggested that, on multivariate analysis, nulliparity is statistically associated with an increased risk of synchronous ovarian malignancy.[12] In another population-based retrospective review, nearly one-half of the women diagnosed with endometrial carcinoma below the age of 45 years required adjuvant radiotherapy after surgico-pathologic staging. Only 18% of women below the age of 45 years diagnosed with endometrial carcinoma were eligible for conservative management had it been considered on the basis of strict clinico-pathological criteria.[7]

Fertility issues

Most women who are diagnosed with endometrial carcinoma at a younger age also have risk factors associated with subfertility. Obesity, hyperandrogenism and polycystic ovarian syndrome are all associated with chronic anovulation. Nearly one-half of the number of women diagnosed with endometrial carcinoma below the age of 45 years are nulliparous.[2,12] This proportion is probably as high as 70% when endometrial carcinoma is diagnosed below the age of 40 years.[3] This carefully selected subset of women diagnosed with complex atypical hyperplasia (CAH) and endometrial carcinoma who are managed conservatively because of desire for future fertility should ideally be co-managed with specialists in reproductive medicine. Assisted reproductive techniques increase the chance of successful conception and also decrease the interval to conception. This is important because women with CAH or endometrial carcinoma who are managed conservatively have a high rate of recurrence of these lesions when the hormone therapy is discontinued.

Conservative management of endometrial cancer in young women

Pre-treatment evaluation

Selection of women for conservative management of endometrial carcinoma should be based on strict criteria. A detailed history will identify women who may require genetic testing for HNPCC. Diagnostic workup, including hysteroscopy, dilatation and curettage, and diagnostic imaging will help in determining the grade and extent of the disease. Tumour grade, depth of myometrial invasion, lymphovascular space invasion and histology are strong predictors of outcome after management of endometrial carcinoma.[14] This is applicable especially when considering conservative management options for women diagnosed with endometrial carcinoma. A combination of these diagnostic modalities will help in assessing these predictors and provide a surrogate for surgico-pathologic staging.

Endometrial sampling and histological review

Adequacy of endometrial sampling is important when planning conservative management of endometrial carcinoma. Although office-based endometrial sampling may be adequate for the diagnosis of endometrial carcinoma, a sample obtained through formal dilatation and curettage may provide further information. Endometrial carcinoma diagnosed on a dilatation and curettage specimen

is less likely to be upgraded on final pathology compared with one obtained through office sampling techniques.[20,21] The role of a diagnostic hysteroscopy along with dilatation and curettage remains controversial. Information gained at the time of a diagnostic hysteroscopy is highly operator dependent. Most clinicians would carry out a hysteroscopy at the time of endometrial sampling as a matter of routine. Concerns have been raised about peritoneal dissemination of endometrial cancer cells at the time of hysteroscopy, but no study has shown a prognostic disadvantage to carrying out a diagnostic hysteroscopy at the time of endometrial sampling in women with endometrial carcinoma.[6]

Expert histological review of the endometrial biopsy specimen is absolutely essential because of the difficulty in histotyping and grading of endometrial carcinomas. Significant diagnostic discrepancies have been identified in up to one-quarter of referred patients.[22,23]

Role of molecular biology

Endometrial tissue is sensitive to steroid hormones. Progestogens act on the endometrial tissue by varied mechanisms: they promote cellular differentiation, apoptosis and cell-cycle arrest while inhibiting inflammation and invasion. Two types of progesterone receptors have been described: progesterone α, which is nuclear and progesterone β, which shuttles between the nucleus and the cytoplasm. Progesterone β is probably the more important of the progesterone isoforms when considering the effect of progestogens in management of endometrial cancer. Progesterone β is more abundant in the endometrial glands. Both progesterone α and progesterone β are likely to be required for endometrial differentiation in endometrial cancer cell lines through distinct mechanisms: progesterone α induces cell senescence and progesterone β induces secretory differentiation. Both isoforms promote apoptosis and induce cell-cycle inhibition. Progesterone β seems to be the principal growth inhibitor of the human endometrial cancer cell growth *in vitro*. The functions of both these progesterone isoforms, however, are still under investigation, and the possibility that progesterone β can actually be a proliferative signal has not been entirely ruled out.[24] Although expression of progesterone is positively correlated with response to progestogen therapy, not all women with progesterone-rich tumours respond to progestogen treatment. One study reported a 72% overall response in women with progesterone-rich tumours, but only 12% response in women with progesterone-poor tumours.[24] Continuous use of exogenous progestogens downregulates both oestrogen receptors and progesterone receptors. This, theoretically, could limit the duration of efficacy of progestogen therapy. Routine testing for progesterone in the dilatation and curettage specimen from women with well-differentiated endometrial carcinoma has been advocated before considering conservative management.[8,25,26]

DNA ploidy assessment has been used in past as a triage tool when deciding on the need for adjuvant treatment for women who have undergone surgical management of endometrial carcinoma. In a retrospective analysis, among women with 'low risk' stage 1 endometrial carcinoma, the recurrence rate was 12.5% for aneuploid tumours compared with 2.1% for diploid tumours.[27] The DNA ploidy studies in this review were carried out on hysterectomy specimens and not correlated with curettage tissue. Further studies are needed to clarify the role of DNA ploidy studies in planning conservative management of endometrial carcinoma.

Phosphatase and tensin homolog (*PTEN*) gene, DNA mismatch repair gene MLH1 and phospho-AKT expression are other immunohistochemical markers that have been studied in predicting response to conservative treatment of complex atypical endometrial hyperplasia and endometrial carcinoma, with varying degree of success. *PTEN* gene and phospho-AKT expression are associated with good response to progestogen therapy. Expression of MLH1 gene in tissues with CAH are associated with treatment failure and a high risk of progression to endometrial carcinoma.[28]

Role of diagnostic imaging in planning conservative management of endometrial carcinoma

Depth of myometrial invasion and cervical extension. Although most young women with endometrial carcinoma present with grade 1 disease limited to the endometrium, a significant proportion will have disease invading into the myometrium or extending beyond the uterine corpus. The risk of lymph-node involvement with grade 1 disease has been estimated to be 3–5%; however, more recent reviews have suggested minimal risk of lymph-node involvement with grade 1 disease as long as the disease is

limited to the inner half of the myometrium.[15] Also one in five women with presumed stage 1 disease will be upstaged after surgico-pathological evaluation.[15] This emphasises the importance of careful pre-treatment evaluation of women who are likely to be offered conservative management. The risk of pelvic lymph-node metastases increases with increasing depth of myometrial invasion.[14]

Pre-treatment imaging should be able to rule out adnexal pathology reliably before a conservative management approach can be offered.

Transvaginal sonography (TVS) is similar or even marginally better than MRI in predicting deep myometrial invasion and cervical extension.[29] The adnexae can also be evaluated with reasonable accuracy. Its inability to evaluate pelvic and para-aortic lymph-node status, however, limits its applicability in the evaluation of women being considered for conservative management of endometrial carcinoma.

Computed tomography scanning has a limited role in pre-treatment assessment when planning conservative management of endometrial carcinoma. The sensitivity of a computed tomography scan in predicting depth of myometrial invasion and cervical extension is 10% and 9%, respectively. Its sensitivity in predicting lymph-node metastases, however, is reported to be around 50%.[30,31]

The better image definition obtainable with MRI is enhanced with techniques such as dynamic contrast-enhanced MRI and diffusion-weighted MRI. The latter enables characterisation of tissues based on their water diffusion properties. The former may be helpful in diagnosis and estimation of endometrial disease when used alone or in combination with dynamic contrast-enhanced MRI.[32] Reports on the accuracy of MRI in predicting depth of myometrial invasion vary from 46.6% to 93%. Accuracy in predicting the absence of deep myometrial invasion is improving, with negative predictive values of 71–92.3%. A recent clinico-pathologic review of 111 women with endometrial cancer reported an impressively high negative predictive value (95%) for absence of deep invasion for grade 1 endometrial carcinoma. Although the accuracy of predicting any myometrial invasion was reported as 88%, the negative predictive value for grade 1 disease remains poor at 46%.[33] With the use of contrast-enhanced MRI, the specificity in predicting deep myometrial invasion approaches 100%.[34] It can also predict cervical extension of endometrial carcinoma, with a reported diagnostic accuracy of 88–98%. Absence of cervical extension of disease has been reported with 100% specificity and a negative predictive value of 97.7%,[34,35] Potential problems can arise with the assessment of myometrial invasion in the presence of uterine fibroids impinging upon the uterine cavity and in the presence of adenomyosis.

Assessment of regional lymph nodes. Assessment of locoregional lymph nodes by radiological methods is challenging. Lymph nodes greater than 1 cm in size, the presence of central necrosis, or both, are considered suspicious of metastases. In a systematic review examining the performance of various diagnostic modalities in detecting lymphatic spread, MRI was the only diagnostic test that could predict lymph-node metastases with a reasonable degree of accuracy. The sensitivity (0.72) and specificity (0.97) of MRI was similar to that achieved by sentinel node biopsy, 0.79 and 0.96 respectively.[31] Magnetic resonance imaging can identify lymph-node metastases in almost all cases in the presence of central necrosis.[36] Use of newer technologies, such as nanoparticle-enhanced MRI, could potentially improve the sensitivity and diagnostic accuracy.[37] With the use of ultra-small articles of iron oxide in a lymph-node specific contrast agent ferumoxtran-10, the sensitivity and overall diagnostic accuracy is significantly enhanced compared with conventional contrast-enhanced MRI. This technique has been used to identify lymph-node metastases in various other cancers with some success, and may be an important tool when evaluating women with endometrial carcinoma for conservative management.

Positron emission tomography with the glucose analog [18F]-fluoro-2-deoxy-D-glucose has a limited role in the pre-treatment evaluation of women planned for conservative management of endometrial carcinoma. [18F]-fluoro-2-deoxy-D-glucose has low to moderate sensitivity (28.6–60%), albeit a high specificity (96.1–98%) in identifying pelvic and para-aortic lymph-node metastases.[38,39]

Assessment of adnexae. No reliable data are available on the efficacy of any of the radiologic modalities in the assessment of concurrent adnexal pathology in women with endometrial cancer. In a multicentre retrospective review, 9% of women with normal preoperative imaging of the adnexae were found to

have synchronous or metastatic ovarian malignancy. In a study in which all women planned for conservative management underwent MRI as a part of pre-treatment evaluation, 14% were found to have ovarian malignancy. The investigators did not specify whether the ovarian pathology was suspected on pre-treatment MRI.[13]

Role of laparoscopy

The limited success of diagnostic modalities in identifying metastatic disease to the locoregional lymph nodes, and in identifying metastatic or synchronous ovarian pathology, could prompt a debate on the role of laparoscopic evaluation of the peritoneal cavity and the retroperitoneum in women planned for conservative management. Ovarian pathology, when present, was macroscopically visible in 78% of women with early endometrial cancer at the time of laparoscopy.[3] A diagnostic laparoscopy would also allow an opportunity to carry out sampling of lymph nodes if nodal disease is suspected on imaging.

Conservative management options

Progestogens

Progestogens have been used for over 50 years in the management of recurrent endometrial cancer with variable response rates. Progestogens have also been used in the primary treatment of endometrial cancer in women with comorbidities who are at high risk for surgery and anaesthesia. Progesterone treatment acts by suppressing cell proliferation in endometrial carcinoma through tumour cell differentiation.[40] Although it has been suggested that women who are likely to respond do so within 12 weeks of starting oral progesterone therapy, some evidence suggests that complete response can take up to 9 months.[41,42] In another review, 76% of women had a complete response to medical treatment, whereas the remaining 24% never responded to progestogens. One-third of the tumours, which initially responded to oral progestogens, recurred. The mean time to relapse was 20 weeks after cessation of treatment. The response rate for repeat treatment with progestogens was as high as 80%.[43] The response rates are similar to those reported by others in smaller case studies and summarised by Cade et al. in[44] a recent review (Fig. 2).

Oral progestogens

Medroxyprogesterone acetate (MPA) in doses of 200–600 mg a day and megesterol acetate 40–160 mg a day have been used in the conservative management of endometrial carcinoma. No randomised-controlled trials have been published, and hence no evidence-based guidelines are available on the optimal dose or duration of treatment. The recommended dose that achieves maximal response has to be balanced against patient tolerance and potential side-effects, especially in the setting of associated comorbidities, such as diabetes and hypertension. The reported incidence of obesity (BMI greater than 30) ranges from 29–62%, and the incidence of associated diabetes is 5–27%.[3] In our institute, we use MPA in a dose of 200 mg twice daily with or without levonorgestrel intrauterine system.[44] In a widely quoted review of 81 women with early endometrial cancer treated conservatively, 76% responded with a median time of 12 weeks. Overall, 58% of women had a complete response and 23% never responded. One-quarter of the women who responded to hormonal therapy experience a recurrence in median time of 19 months (range 6–44 months).[45] In a recently reported multicentre prospective study on conservative management of well-differentiated endometrial carcinoma, a response rate of 55% was achieved after 26 weeks of oral MPA in the dose of 600 mg a day. Of these, 90% of women achieved complete response after 16 weeks of treatment. More importantly one-half of women with endometrial carcinoma who achieved a complete response to progestogen treatment had a recurrence after a mean progression-free interval of 34.6 months. Ovarian malignancy was identified in two out of 10 women who underwent bilateral salpingo-oophorectomy for non-responding or recurrent disease. Another woman developed peritoneal carcinomatosis 2 years after initial MPA treatment.[46]

Side-effects of progestogen therapy. It is important to consider side-effects when prescribing oral progestogens. These include weight gain, appetite stimulation and venous thromboembolism. Most

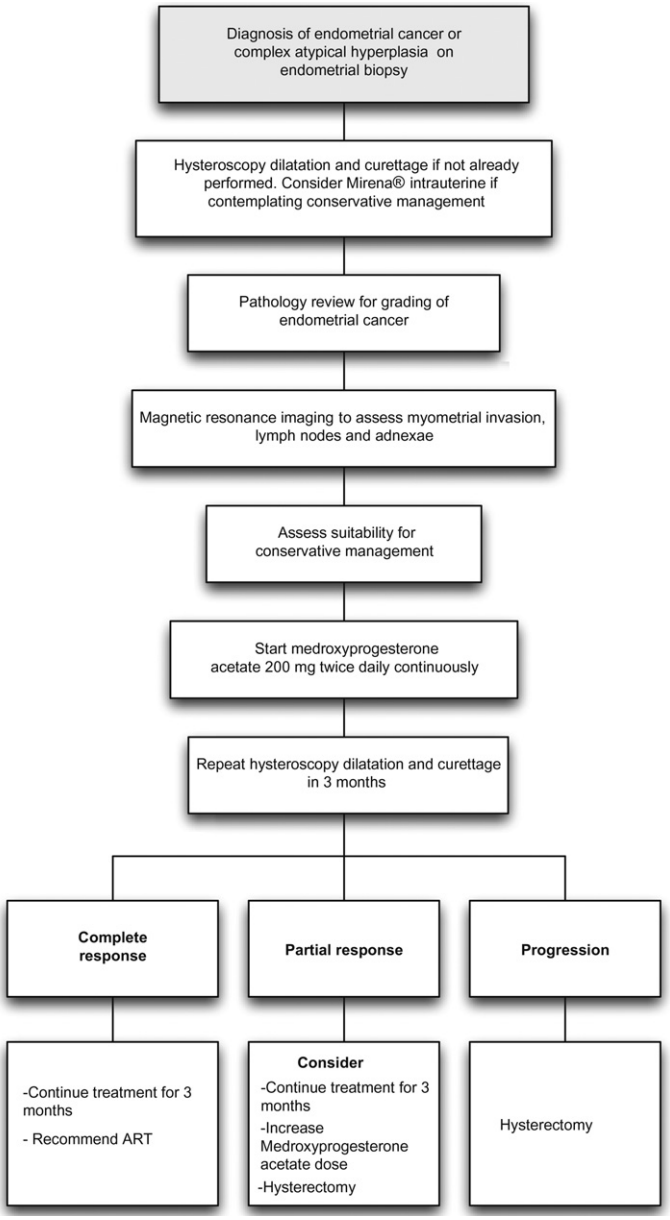

Fig. 2. Recommended algorithm for conservative management of endometrial cancer in young women.

studies report good tolerance to high-dose progestogens or do not report any serious side-effects. In one prospective study, use of 600 mg/day of MPA, only three out of 45 women experienced clinically significant weight gain and liver dysfunction.

Levonorgestrel-releasing intrauterine system

The use of levonorgestrel-releasing intrauterine system (LNG-IUS) in managing endometrial cancer was initially described in cases in which severe co-morbidities precluded the standard surgical

management.[47] Response rates of up to 75% were reported. Importantly, the intrauterine system used (Progestasert®) in this review released 65 μg/day compared with more widely available LNG-IUS (Mirena®) that releases 20 μg of levonorgestrel per day.[47]

The LNG-IUS has been used along with gonadotropin releasing hormone analogue with some success. In a prospective observational study, just over one-half of the study population with well-differentiated endometrial carcinoma achieved complete response. One-quarter of the women experienced progressive disease while on treatment. Interpretation of the results of this study is limited by small numbers.[13]

The use of LNG-IUS alone for conservative management of endometrial carcinoma cannot be recommended on the basis of current evidence. It may be reasonable to insert a LNG-IUS at the time of initial hysteroscopy while treating with oral progestogens. No evidence is available on any additional therapeutic benefit with this approach.

Women with complex atypical hyperplasia of endometrium tend to have better response rates when treated with LNG-IUS compared with its use in the treatment of endometrial carcinoma.[13]

Hysteroscopic resection followed by progesterone therapy

An innovative method for conservative management of endometrial carcinoma has been described that includes hysteroscopic resection of the endometrial tumour along with the myometrium underlying the tumour followed by oral megesterol acetate 160 mg a day. The investigators describe a complete response in all six women, with no reported complications.[26] Five successful pregnancies in four women were reported. This technique can only be recommended with small discrete lesions evident on hysteroscopy. The possible complications of hysteroscopic dissemination of disease, post-operative intrauterine adhesions and complications during pregnancy and delivery related to hysteroscopic resection also need to be considered and evaluated in a larger study.

Monitoring response to progestogen therapy

The evidence supporting conservative management of endometrial cancer is limited to relatively small retrospective studies, which precludes any attempt at producing evidence-based guidelines or management protocols. Most women who respond to progestogen therapy do so within 12 weeks of starting treatment (range 4–60 weeks).[45] Others have suggested that response to hormonal treatment can take as long as 9 months and that consideration should be given to persevere with treatment in the absence of response after 3 months of treatment.[42]

We recommend carrying out a hysteroscopy and curettage after 3 months. On the basis of this result, further endometrial sampling can be carried out 3–6 months later in the premenopausal women. We further recommend continuing the treatment for another 3 months after a negative biopsy to consolidate the gains of medical treatment while the woman seeks the opinion of a reproductive medicine specialist.

A biopsy result with no initial evidence of response should prompt a further discussion with the woman. It may be reasonable to continue with the medical management for a further period of 3 months.[48] In a recent review, the mean interval for evidence of persistent or progressive disease was 6.7 months for 57 non-responders. It may be reasonable to discuss definitive surgical management after 6 months of conservative management in the absence of pathologic response.[49]

Risks of conservative management

The biggest concern with conservative management of endometrial carcinoma is disease progression while on treatment or after initial response to medical treatment. One-quarter to one-half of women who initially respond to hormonal treatment will experience a recurrence after a variable length of time (Table 1).[50] Four cases of fatal recurrences of endometrial cancer after complete response to medical treatment have been documented.[28,43] The risk of under-staged disease because of using surrogate markers for surgical staging, risk of concomitant ovarian malignancy and the risk of

Table 1
Review of literature on conservative management of endometrial cancer. Adapted with permission.[50]

Reference (Year)	*N*	Type and dose of progestagen	Results
Susumu et al. (2001)	14	Medroxyprogesterone acetate 600 mg once daily	86% response over 8 weeks, 58% recurrence; 14% no response (had myometrial invasion)
Montz et al. (2002)	12	Levonorgesterol intrauterine device	64% biopsy negative at 6 months; 75% biopsy negative at 12 months
Wang et al (2002)	9	Megesterol acetate, tamoxifen, gonadotrophin releasing analogue	89% complete response; 50% subsequent recurrence; 11% no response.
Ramirez et al (2004)	81 (literature review)	Review of all with oral or intramuscular hormonal treatment	76% response with median time of 12 weeks; 24% initial response then recurrence (median time 19 months); 23% no response
Dhar et al (2005)	4	Levonorgesterol Intrauterine device	25% complete regression in 6 months; 75% no response in 6 months (one had myometrial invasion)
Wang et al (2006)	6	Oral (dose not specified)	67% total response; 50% recurrence between 10 and 12 months; 33% no response
Yamazawa et al (2007)	9	Medroxyprogesterone acetate 400 mg once daily	78% complete response in 6 months; 22% partial response; 22% recurrent disease between 10 and 22 months
Chiva et al (2008)	133 (literature review)	Review of all hormonal treatment	76% complete response after average of 12 weeks; 34% of these had a recurrence; 24% no response; four published deaths of women treated conservatively.
Eftekhar et al (2009)	21	Megesterol acetate 160–320 mg once daily	86% response rate; 17% recurrence.

progression should be clearly explained to the woman when opting for conservative management of endometrial carcinoma.

Complex atypical hyperplasia of endometrium

A discussion on the management of well-differentiated endometrial carcinoma would not be complete without the mention of CAH of endometrium. This is considered as the precursor lesion for type 1 endometrial carcinoma. As many as 48% of women diagnosed with CAH are believed to have a co-existent focus of endometrium carcinoma. The proportion of women with co-existing malignancy rises with increasing age.[51] There is reason to believe that the incidence of CAH in young women is rising in keeping with the rising incidence of endometrial carcinoma. We believe that management of CAH in young women desirous of future fertility should be along the lines of conservative management of well-differentiated endometrial carcinoma. The response rates after medical management are better, in the range of 80–100%, even when the LNG-IUS alone is used.[52]

Endometrial cancer in young women associated with Lynch syndrome

Hereditary non-polyposis colorectal cancer (HNPCC) syndrome or Lynch syndrome is an autosomal dominant disorder caused by mutations in a family of DNA mismatch repair genes (MSH2, MLH1, MSH6, PMS2). Individuals with HNPCC have a genetic predisposition to developing different kinds of cancers. Apart from the risk of colorectal cancers, women with HNPCC syndrome have a 40–60% lifetime risk of developing endometrial cancer and about 12% lifetime risk of developing ovarian cancer.[4] Young women diagnosed with endometrial carcinoma are at a high risk of being diagnosed with HNPCC syndrome and need to be referred to familial cancer clinics for risk assessment and need for genetic testing.

It has been suggested that young women with HNPCC syndrome who are diagnosed with endometrial carcinoma should not be considered for conservative management.[7] Successful pregnancy after conservative management of endometrial carcinoma in a woman with Lynch syndrome has been

reported, although the long-term follow up was not described.[53] Studies are sparse on long-term survival of women who develop endometrial carcinoma in association with Lynch syndrome compared with those with endometrial carcinoma from the general population. In a retrospective review, it was suggested that the two groups have similar 5-year survival.[54] A recent study, however, has questioned this and suggested more aggressive management may be needed.[55] On the basis of current evidence, we do not recommend conservative management of endometrial carcinoma associated with HNPCC syndrome.

Selection of women for conservative management

Women desirous of future fertility who are offered conservative management options should be carefully evaluated. Selection criteria for offering fertility-sparing treatment options should be stringent, and the women should be extensively counselled about the risks. The consultation should include a discussion of the difficulties in grading endometrial cancer on curettage specimens and in predicting the depth of myometrial invasion on imaging studies. Furthermore, the couple need to be aware that no randomised-controlled studies have been conducted on the type of progestogens, the dose, the scheduling, and the route of and length of administration.

Criteria for conservative management

Only women meeting the following criteria should be offered conservative management options: (1) women diagnosed with endometrial cancer under 40 years; (2) planning on achieving pregnancy soon after disease regression; (3) well-differentiated endometrioid adenocarcinoma on expert histological review; (4) no evidence of myometrial invasion, cervical extension and pelvic or para-aortic lymphadenopathy on pre-treatment MRI; (5) normal adnexae on MRI; a diagnostic laparoscopy should be considered if there is any doubt of adnexal pathology; and (6) no medical contraindications to high-dose oral progestogens.

Women opting for conservative management should be counselled that medical treatment is not the standard management and should agree to comply with the follow-up protocols. The potential risks of repeated endometrial curettage and the risk of Asherman's syndrome should be explained. Referral to reproductive medicine specialists for consideration of assisted reproductive techniques should be discussed and offered. A suggested algorithm for evaluating women with endometrial carcinoma planned for conservative management is detailed in Fig. 2.

Obstetric outcomes after conservative management of endometrial carcinoma and complex atypical hyperplasia

The main aim of conservative management of endometrial carcinoma is to achieve successful pregnancy after disease regression. Most reports are limited to single patient case reports or small case studies, with varying degrees of success. Among case studies, pregnancy rates of 50–75% have been reported, with take home baby rates of 30–50%.[8,28,49,56] Others have reported higher pregnancy and take home baby rates as high as 80%.[42] Pregnancy rates are higher with the use of assisted reproductive techniques than with spontaneous conceptions.[28] As most of the women diagnosed with endometrial carcinoma at a young age also have risk factors associated with subfertility, the implementation of assisted reproductive techniques increases the chance of successful conception and also decreases the interval to conception.[57]

Hysterectomy after completing childbearing

Fertility-sparing conservative treatment of endometrial cancer deviates from the standard management of care, and the risk of recurrence of endometrial carcinoma is significant; several fatal recurrences have been reported after conservative management of presumed early stage disease.[28] The discussions with the woman, reasons for conservative management, results of investigations, and follow-up plans should be carefully documented and communicated to the primary care providers. A

willingness to proceed with definitive management of the endometrial carcinoma in the form of hysterectomy and bilateral salpingo-oophorectomy after child bearing is complete should be established before embarking on conservative management. In a literature review, although most women had a lasting response to conservative management, recurrences were diagnosed as late as 3-4 years after conservative management. Some of the tumours that recurred did so in absence of any risk factors.[56]

Conclusion

Endometrial cancer is increasingly being diagnosed in women aged 40 years or younger. Surgical management in the form of total hysterectomy and bilateral salpingo-oophorectomy without lymph-node dissection is the standard treatment for any woman with endometrial cancer. Conservative management with hormonal therapy may be considered in carefully selected women with well-differentiated early stage endometrial cancer. This treatment option deviates from standard management and requires careful pre-treatment evaluation and counselling. Conservative management of endometrial cancer in young women should only be carried out in a multi-disciplinary team setting.

Practice points

- Standard management of endometrial carcinoma in any age group is hysterectomy, bilateral salpingo-oophorectomy with or without pelvic para-aortic lymph-node dissection.
- Conservative management of endometrial carcinoma may be a therapeutic option in carefully selected women with well-differentiated endometrial cancer in the absence of any myometrial invasion or adnexal disease seen on imaging.
- About one-half of women selected for conservative management respond to high-dose oral progestogens.
- One-quarter of women who respond initially to oral progestogens will experience a relapse.
- Hysteroscopy and dilatation and curettage should be carried out every 3 months to assess treatment response until complete regression is established. Further testing may be carried out at 6 monthly intervals in the presence of a sustained response.
- In the absence of pathologic response to hormonal therapy after 6 months, it is reasonable to offer definitive surgical management.
- Women opting for conservative management should be aware that hormonal therapy is not the standard form of management. Potential adverse outcomes should be taken into consideration.
- Multidisciplinary management with a team of reproductive medicine specialists should be considered.
- Once child bearing is complete, standard surgical management should be offered.

Research agenda

- Comparison of different doses and types of progestagens in the conservative management of endometrial cancer.
- Role of progesterone-coated intrauterine devices in the conservative management of endometrial cancer.
- Molecular markers to differentiate atypical hyperplasias from true invasive endometrial cancers.

Conflict of interest

None declared.

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