

ORIGINAL RESEARCH

Short and long-term outcomes of endometrial cancer and atypical endometrial hyperplasia management in young women

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Abstract

Objective: The incidence of endometrial cancer in young women is increasing. Since survival after management is in most cases excellent, the focus on long-term patient reported outcomes (PROs) is crucial. Herein we examine the characteristics and oncological and reproductive outcomes of young women with endometrial cancer. **Methods:** We have identified all women under 45 years of age treated at the University Medical Centre Maribor between the years 2008–2020. Women were contacted to evaluate the endometrial cancer specific PROs using the EORTC QLQ-EN24 questionnaire. **Results:** Endometrial cancer and atypical endometrial hyperplasia were diagnosed in women younger than 45 years in 5.1% women and in 5.3% women respectively. Fourteen women (44%) under 45 years were eligible for fertility sparing procedures and only 6 of them (43%) opted for this approach. Women who opted for fertility sparing procedures were significantly younger ($p < 0.001$) with a median age of 31.0 (29–35) versus 42.5 years (34–45) in women opting for standard treatment. A significant proportion of women opting for fertility sparing treatment (67%) were nulliparous ($p < 0.014$) at time of diagnosis. Considering PROs, a high level of reported back/pelvic pain and tingling/numbness in the limbs was reported in our group of women. **Conclusions:** Young women with endometrial cancer should be offered counselling on the possibility of fertility sparing procedures. Future research should focus on long term PROs and mechanisms of improving them.

Keywords

Endometrial cancer; Quality of life; Fertility sparing therapy

1. Introduction

Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries and the second most common in developing countries [1, 2]. It accounts for 3.6% of all cancers in females and it generally affects postmenopausal women, with a mean age at diagnosis of 62 years [1, 3]. Approximately 5% of women diagnosed with EC are younger than 40 years, and around 10% to 15% are younger than 50 years [1, 4, 5]. From 2006 to 2010, the incidence rates of EC increased by 2.6% per year in women aged 50 years and older and by 1.5% per year in women younger than 50 years [6]. An increasing incidence trend in young women has also been observed in Slovenia [7].

The occurrence of EC at a young age has been associated with prolonged unopposed estrogen exposure. This is most commonly in women with hormone-related disorders, obesity, infertility or polycystic ovarian syndrome [8, 9]. For decades, EC has been traditionally classified into two main types. Type I is the much more common endometrioid adenocarcinoma (80–90%). It represents 75–85% of cases in

young women who have unopposed estrogen exposure. The tumours are usually well differentiated and have a favourable prognosis. Type II comprises non-endometrioid subtypes such as serous, clear-cell and undifferentiated carcinomas, as well as carcinosarcoma/malignant-mixed Müllerian tumour (10–20%). These tumours are less differentiated and have a poor prognosis [3, 10]. A precancerous lesion of type I EC is atypical endometrial hyperplasia (AEH), but 29% of such cases progress to EC within several years [4, 11].

Most young women present with Type I EC, which is well differentiated and at early stages with no invasion or superficial myometrial invasion [1, 12]. In fact, in this patient group, when the disease is well differentiated and confined to the uterus, the 5-year survival rate is 96% [3]. However, the standard treatment of early-stage EC includes a total hysterectomy with a bilateral salpingo-oophorectomy resulting in total loss of fertility [7, 13]. This is an especially important question for young patients that wish to preserve fertility. In such patients the evaluation of fertility sparing therapy (FST) should be considered. Recommendations have not widened the pool of patients that can potentially be considered for FST

in the last years. The recently updated ESGO/ESTRO/ESP guidelines on endometrial cancer [14] recommend that FST should only be considered in patients with AEH/EIN or grade 1 endometrioid EC without myometrial invasion and without genetic risk factors.

Considerations of treatment options and treatment aggressiveness in young patients with EC include considerations on fertility preservation as well as long term patient outcomes. A meta-analysis of patients reported outcomes in patients with EC shows that obesity was associated with lower quality of life (QoL) and physical function. Better QoL outcomes were also reported if patients had minimally invasive instead of open surgery [15].

The aim of this study was therefore to evaluate the outcomes of treatment in young patients with EC as well as their patient-reported long-term outcomes.

2. Materials and methods

2.1 Patients

This study included a retrospective tertiary hospital, single institution study identified through a patient record analysis patient under 45 years of age treated for EC or AEH between the years 2008 to 2020. We collected demographic and clinical data available from our patient records. Clinical staging was performed according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system [16]. We evaluated the pre-treatment diagnostics as well as mode of therapy and long-term quality of life outcomes using the EORTC QLQ-EN24 questionnaire. All women regardless of time of treatment were invited by post to complete the EORTC QLQ-EN24 questionnaire and return it within a timeframe of two weeks to our clinic.

2.2 Instrument

For the evaluation of long-term quality of life related outcomes, the EORTC QLQ-EN24 instrument was developed specifically for EC patients. It was developed to incorporate functional scales on sexual interest, activity and enjoyment and the Likert scale symptom items. The symptom items include the evaluation of lymphedema presence, urological and gastrointestinal symptoms, the assessment of body image, sexual problems, pain symptoms, tingling/numbness, hair loss and taste change [17]. The EORTC QLQ-EN24 questionnaire was translated to the Slovenian language and pilot tested under the supervision and according to the standard procedure of EORTC. The instrument has been used with the permission of EORTC.

2.3 Statistical analysis

The quantitative data was evaluated using descriptive statistics. First, the distribution of continuous variables was checked using the Shapiro-Wilk test. Since continuous variables were non-normally distributed, appropriate non-parametric tests were used. For categorical variables, absolute and relative frequencies were reported. Categorical variables were analysed using the Chi-square test and the Mann-Whitney

U test was used to compare the differences in dependent variables. Data analysis was performed using SPSS Statistics 23.0, IBM (Armonk, New York, USA).

3. Results

3.1 Patient characteristics

Overall, between 2009–2020, 29 out of 614 women with EC (4.7%) and 3 out of 56 (5.3%) women with AEH were younger than 45 years at time of diagnosis. Patient characteristics are presented in Table 1.

One woman (3.1%) who decided for standard surgical management experienced disease recurrence. One woman (3.1%) died during the follow up period from non-disease specific reasons. There was no significant association between the reasons for diagnostic work-up and the final FIGO disease stage ($p = 0.302$).

3.2 Management of women with EC or AEH

Twenty-six women (81.3%) opted for standard surgical management. Minimally invasive surgery was performed in 17 women (65.4%), 8 women had an open surgical procedure (30.8%) and in 1 woman (3.8%) conversion from laparoscopy to laparotomy had to be performed due to obesity. Among the women treated with surgery, lymph node dissection (LND) was performed in 18 women (69.2%). Five women had sentinel node biopsy (SNB) and 13 had bilateral or unilateral lymph node dissection. Patients attempting FST were significantly younger ($p < 0.001$) and were initially seen because of abnormal uterine bleeding ($n = 1$) or infertility ($n = 4$). The presenting symptom data for one patient was missing. After comprehensive counselling, 6 out of 32 women (15.6%) opted for fertility sparing management.

3.3 Fertility sparing treatment

Twenty-one women were pre-operatively classified as Type I EC grade 1 ($n = 17$) or as AEH ($n = 4$). Among these women, a suspicion of superficial myometrial invasion ($n = 6$) or deep myometrial invasion ($n = 1$) was made by transvaginal ultrasound examination, which is generally considered an exclusion criterion for fertility sparing management according to the current guidelines. The remaining 14 women (44%) were eligible for FST. Among these, 6 (42.8%) decided for this approach and 8 women decided for standard surgical treatment. The characteristics and outcomes of women opting for FST are depicted in Table 2. Women opting for FST were significantly younger with a median age of 31.0 years (29–35) versus 42.5 years (34–45) ($p < 0.001$) and in most cases nulliparous (66.7% vs. 11.5%, $p < 0.014$).

3.4 Long term patient related outcomes

The response rate to the long-term follow up questionnaire was 31%. All participants who returned the questionnaire answered all the obligatory items. The questions relating to sexual activity in the last 4 weeks were answered affirmatively by 8 women (89%). The outcomes are reported in Table 3.

TABLE 1. Patient characteristics of women younger than 45 years diagnosed with endometrial cancer or atypical hyperplasia (n=32).

Age at time of diagnosis (median, range)	39.8 years (min–max: 29–45 years)
Parity (N, %)	
Nulliparous	7 (21.8%)
Multiparous	25 (78.2%)
Reason for diagnostic work up (N, %)	
Abnormal uterine bleeding	19 (59.4%)
Infertility	5 (15.6%)
Abdominal pain	2 (6.3%)
Incidental TVUS changes	2 (6.3%)
Abnormal prolonged vaginal discharge	1 (3.1%)
Missing data	3 (9.3 %)
Pre-operative histological EC type (N, %)	
Type I	25 (78.1%)
Type II	1 (3.1%)
Atypical Hyperplasia	4 (12.5%)
Treatment for presumed benign condition	2 (6.3%)
Pre-operative histological grade (N, %)	
G1	17 (53. %)
G2–3	6 (18.8%)
missing data	4 (12.5%)
N/A	5 (15.6%)
TVUS assessed myometrial invasion (N, %)	
No invasion	12 (37. %)
Superficial invasion	16 (50%)
Deep invasion	4 (12.5%)
Final FIGO disease stage (N, %)	
IA	20 (62.5%)
IB	4 (12.6%)
II	2 (6.2%)
III	2 (6.2%)
Atypical endometrial hyperplasia	4 (12.5%)

N/A—not applicable due to histological subtype of endometrial cancer or presumed benign disease.

4. Discussion

In our population of young women with EC and AEH, standard surgical treatment was most commonly used (81.3%). Less than half of all women eligible for fertility sparing management decided for this approach. These women were significantly younger, with none above the age of 35. Four out of six women were also childless.

According to the previously published data, most young women with EC presented with symptoms of abnormal uterine bleeding [10]. All women with abnormal uterine bleeding require diagnostic evaluation of bleeding and EC is likely to be diagnosed in early stages. However, it is very important to note that a large proportion of women (40%) were seen due to other indications. Our data has shown that especially in women seen due to infertility, endometrial cancer can occur, and attention needs to be focused towards screening for endometrial pathology during infertility diagnostics.

There are different approaches to FST in endometrial cancer. The initial therapy prior to an attempt at pregnancy includes treatment with different combinations of oral progestins, levonorgestrel intrauterine (LNG-IUS), metformin and hysteroscopic resection (plus oral progestins or LNG-IUS) [5, 18]. Important considerations in presenting women with

the option of FST is also counselling on therapeutic efficacy of the different approaches. Best outcomes in a retrospective study by Maggiore *et al.* [19] showed, complete response to therapy was best in AEH (89%), worse in EC Grade 1 (81%) and the worst in EC Grade 2 (75%). After extensive counselling about the possible risks and benefits, only a third of all eligible women opted for fertility sparing management at our institution. Nonetheless, this ratio is comparable to a large cohort published by Harrison *et al.* [20], where 79.6% of all women opted for standard surgical procedures. In our cohort, all women opting for fertility sparing procedures required medically assisted reproductive procedures to conceive. Four out of six women (67%) achieved a pregnancy. This is higher than usually reported rates of live birth after FST [21]. There were 3 live births in 4 women. One woman who conceived, unfortunately experienced a spontaneous miscarriage in early pregnancy. This indicates that spontaneous conception after FST for EC can be difficult and most often, medically assisted reproduction is needed. Research shows, that attempts to conceive after undergoing FST should be done immediately after a confirmed complete remission of EC/AEH [22]. Previous studies show that a about a third of women opting for FST had a history of infertility [23]. As the goal of FST is conception

TABLE 2. Characteristics and outcomes of women opting for fertility sparing management.

	Age	Reason for work-up	Tumour histology	Parity	Treatment	ART	Outcomes	Final surgical treatment
Patient 1	30	Infertility	EEC	0	MPA and levonorgestrel IUS	yes	1 live birth after ART	/; attempting 2nd pregnancy
Patient 2	29	Infertility	EEC	0	MPA	yes	2 live births after ART	4.5 years after diagnosis; hysterectomy
Patient 3	29	Infertility	AEH	1	GnRha therapy	yes	No live birth, 2 miscarriages after ART	/; attempting pregnancy, regular endometrial biopsies
Patient 4	33	AUB	EEC	1	MPA	yes	1 live birth after ART	1.9 years after diagnosis; hysterectomy
Patient 5	35	AUB	EEC	0	MPA and levonorgestrel IUS	yes	Currently still attempting conception (ART)	/; attempting pregnancy, regular endometrial biopsies
Patient 6	32	Infertility	EEC	0	MPA	No	unsuccessful ART prior to EC diagnosis	1.5 years after diagnosis; hysterectomy

EEC, endometrioid endometrial cancer; AEH, atypical endometrial hyperplasia; /, no final surgical treatment.

TABLE 3. Health related symptoms evaluated by EORTC QLQ-EN24 scale.

Health related symptoms	median value, range
Age at time of study	45 (37–51)
Lymphoedema	0 (0–67)
Urological symptoms	0 (0–67)
Gastrointestinal symptoms	27 (0–54)
Body image problems	17 (0–67)
Sexual/vaginal problems	17 (0–56)
Back/pelvis pain	34 (0–100)
Tingling/numbness	34 (0–100)
Muscular/joint pain	34 (0–67)
Hair loss	0 (0–67)
Taste change	0 (0–34)
Sexual interest	34 (0–67)
Sexual activity	34 (0–67)
Sexual enjoyment	67 (0–100)

and childbirth, improvement of conception rates are needed. Through the understanding that women often have already had difficulty conceiving prior to the diagnosis of EC or AEH and knowledge, that some studies report improved reproductive outcomes with ART [23] in women undergoing FST, higher rates of ART can be expected in women undergoing FST. Factors which can have an impact on conception and are also connected with EC/AEH are polycystic ovarian syndrome (PCOS), obesity or other metabolic syndromes. These factors might also impact endometrial receptivity and represent comorbidities which increase the need for ART [22]. Since there is little data available on the long-term safety of uterine conservation in women with diagnosed EC, early referral to reproductive medicine specialists is warranted in this group of women.

Reproductive outcomes do not seem to differ between patients with grade 1 EC and AEH [24]. Research however

shows that disease persistence was more common in carcinoma patients than patients with endometrial hyperplasia [1, 24]. With the increasing incidence of EC [25], young women need to be counselled on fertility sparing options and the success rates of such treatment.

In light of the safety issue pertaining FST, the dawn of molecular classification in EC has provided us with an opportunity to improve our assessment of women wanting to undergo fertility sparing treatment in EC. The integration of EC molecular classification in the ESGO/ESTRO/ESP guideline [14] represents an important step towards the clinical application of molecular classification in the consideration of FST. However, data to support the impact molecular classification can have on selection of patients suitable to undergo fertility preservation in early stage EC is lacking. The Proactive Molecular risk classifier for Endometrial Carcinoma (ProMisE) evaluated in their cohort 257 women with EC before the age of 50 years [26]. These women mostly had no specific molecular subtype (NSMP; 64%), and in smaller proportions of POLE mutated (POLEmut; 13%), mismatch repair deficient (MMRd; 19%) and with an abnormal p53 expression pattern (p53abn, 4%) subtypes [26]. However, these women did not undergo fertility sparing treatment and were part of a post-hoc analysis, thus not allowing us a full understanding in young women which might be candidates for FST. Women undergoing FST in our study were counselled based on histopathological tumour analysis, since molecular classification was not available at the time. The value of the molecular characterisation needs to be proven in future larger scale studies.

It is likely that most women opting for fertility sparing treatment will fall into the NSMP group of EC, which is also connected with a higher body mass index (BMI) in women under 50 years of age in the analysis performed by Britton *et al.* [26]. Furthermore, a retrospective study including 57 women has shown that MMRd tumours could be associated with lower response to progestin therapy [27]. This means more research will also need to go into understanding the molecular subgroups of EC in young women in order to enable better understanding of safety issues and potential to achieve

complete remission in these women.

Clinicians however, also need to consider the long-term clinical impacts as a recently published study [27] showed, that in women under 40 years, attempting conservative treatment the rate of disease recurrence was higher and progression-free survival worse, which was directly attributed to fertility sparing procedures.

An important part of further decision making in treatment of young patients with endometrial cancer, who have excellent overall survival [27] should also be the long-term outcomes. These outcomes are not only oncological outcomes but also the patient reported outcomes. In our analysis, only a very small group of women (28%) completed the questionnaire of long-term health related symptoms impacting their quality of life. Therefore, our data should be validated in larger groups of young women with EC and should be interpreted with caution. The data show a low prevalence of lymphoedema, urological problems, body image problems and sexual/vaginal problems. The data show comparable reports of health-related problems in comparison to Greimel *et al.* [17] in most domains, but showed a higher level of reported back/pelvic pain and tingling/numbness in the limbs. This should be further explored in larger evaluations as it might be an important further aspect for interventions in order to improve the long-term patient reported outcomes [15, 28]. Very little knowledge is still available on the evidence-based support to improve patient related outcomes. Especially in gynaecological cancers, as women report not only a decline of physical, but also sexual quality of life [29], more focus should be put towards evaluation as well as support to improve quality of life after primary cancer treatment.

In light of the low number of women attempting FST, final conclusions from data should be evaluated with caution. The presented data shows a retrospective, mono-institutional experience of the management of young women with EC and AEH. Our data is well in accordance with previous studies but should be informed by larger prospective trials in FST.

5. Conclusions

In conclusion, the incidence of endometrial cancer in young women is on the rise. This is partly related to the modern lifestyle and increasing rates of obesity. This group of women requires special considerations when counselling about the management options. Since long-term survival is in most cases excellent, quality of life after treatment needs to be considered. Special focus needs to be aimed towards discussing ovarian and uterine conservation in younger women. Improvements in diagnostic procedures, introduction of additional biomarkers to better characterise the disease and better clinician and patient education is likely to improve the management decisions and quality of life in this group of women in the future.

AUTHOR CONTRIBUTIONS

MS—Conceptualization, methodology, formal analysis, data curation, writing—original draft preparation, project administration; DG—Conceptualization, investigation, data curation, writing—original draft preparation; DA—resources,

writing—review and editing; JK—Conceptualization, methodology, resources, writing—review and editing, supervision; All—read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the University Medical Centre Maribor institutional review board (No. UKC-MB-KME-62/20). Project specific patient consent was waived due to the previous consent given by patients to use their anonymized data for research purposes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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