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Original Research Article

Challenges in the management of endometrial cancer and endometrial hyperplasia with atypia in sub-fertile patient: an emerging medical issue-our experience in a tertiary care centre

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ABSTRACT

Background: The cases of endometrial hyperplasia with atypia/endometrial carcinoma with age below 40 years are rising and many are nulliparous at diagnosis. The purpose of the study was to study the oncological and obstetric outcome among young women with above mentioned endometrial pathology treated with fertility preserving approach.
Methods: The retrospective cohort approach included 17 patients who visited Bhagwan Mahaveer Jain Hospital from January 2016 to January 2022 with a diagnosis of endometrial hyperplasia with atypia/endometrial carcinoma who met national comprehensive cancer network criteria. The records of all the patients included in the study have been reviewed retrospectively.
Results: In our study 13/17 (76.47%) patients showed complete response to hormonal treatment. Conception rates are low (23.07%) even after reversal of the malignancy. Thirteen of 17 patients had associated polycystic ovarian syndrome. Three out of 17 (17.64%) had progressive disease, 5/13 (38.46%) cases had disease recurrence after initial remission out of which 3 had rechallenge with progestins with remission again.
Conclusions: Levonorgestrol intra uterine system along with oral progestins is an effective combination as device might be useful in optimising the dose of oral progestins without the need for further escalation of dosage. Levonorgestrol intra uterine device or low dose oral progestins alone should be continued in responders not opting for conception as maintenance hormonal therapy. Hysterectomy should be advised if hormonal treatment fails, and also after completion of childbearing. Myometrial invasion may not be absolute contraindication for fertility sparing treatment. Molecular profiling of endometrial biopsy might help in better prognostication and treatment strategy.

Keywords: Endometrial carcinoma, Endometrial hyperplasia with atypia, Nulliparous, Fertility preservation, Progestins, Original study, Tertiary centre

INTRODUCTION

Although atypical endometrial hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) and endometrial cancer (EC) are usually observed in postmenopausal women, they may also develop, albeit rarely, in women under 40 years of age.[1] The incidence of AH/EIN and EC in this age group has increased in recent years.[2] Around 4% of women with EC are younger than 40 years old.[3,4] Over 70% of them are nulliparous at diagnosis, due to the fact that in the current era women delay their childbearing. The majority of ECs are diagnosed early stage (80% in stage I), with 5-year survival rates over 95%. Most EC cases are sporadic, with

only 5% considered familiar.[5,6] Type I (endometroid – estrogen dependent) cancer is most commonly seen in nulliparous women <40 years. Nulliparity and infertility are classical risk factors for EC. Obesity, polycystic ovarian syndrome (PCOS), anovulatory cycles - all cause hyper estrogenic state which is the main predisposing factor for developing type I endometroid carcinoma.[7]

Fertility preservation is feasible in early endometrial carcinoma in young women – although total hysterectomy with bilateral salpingo-opherectomy is the standard treatment.[5,8-10] Conservative treatment consists of medical management with hormonal therapy – mainly progestins (oral + intra uterine device). Majority of the type I tumours respond to progestins.[5,9-12]

The national comprehensive cancer network (NCCN) guidelines were followed in most of the cases except a few patients with myometrial invasion who were not willing for definitive surgery.[5] Patients were thoroughly informed that fertility sparing treatment is not the standard of care for endometrial carcinoma management.

In the present study we studied the oncological and obstetric outcomes of various fertility preserving treatment comprising mainly a combination of oral progestins and levonorgestrol intra uterine device system (LNG-IUD).

METHODS

The study is a retrospective data analysis of patients visiting Bhagwan Mahaveer Jain Hospital (BMJH) between the period of January 2016 to January 2022 who were diagnosed with endometrial hyperplasia with atypia/endometrial carcinoma on endometrial biopsy. Type 1 EC and hyperplasia is associated with hormonal imbalances with estrogenic stimulation of the endometrium and relative deficiency of progestins as seen in obese and diabetic peri menopausal women who are mostly nulliparous. In young subfertile women, PCOS is known to be associated with unopposed estrogenic stimulation of the endometrium. All case records of women who met the inclusion criteria were studied and analysed.

Inclusion criteria

All patients presenting with endometrial hypersia with atypia/EC who wished to preserve fertility and met the NCCN criteria (except 2 with myometrial invasion who were not willing for definitive surgery and wanted fertility preservation after taking detailed consent) were included.

Exclusion criteria

Patients who did not meet the NCCN criteria were excluded.

It has to be noted that molecular subtyping on the endometrial biopsy was done in the few recent patients. Comprehensive germline mutation panel testing on blood sample was done selectively in the hormonal therapy non-responders.

Magnetic resonance imaging (MRI) scan with gadolinium contrast of the pelvis and abdomen was obtained to determine myometrial invasion and extra-uterine disease status.

Management criteria followed

The patients meeting the above criteria after complete evaluation were started on oral progestins and in the later part of the study also had LNG-IUD inserted. Regular monitoring of the patients was done at 3 months interval mainly with trans-vaginal ultrasound and endometrial biopsy with LNG-IUD in situ. Patients with complete response desirous of fertility were counselled for artificial reproductive technique (ART) to avoid delay in conception and possible risk of recurrence.

Hysteroscopic resection of the tumour and any polyp was carried out first especially for bulky, polypoidal tumours. The patients were started on megesterol acetate 160 mg/day along with LNG intra-uterine device (Mirena) which was started in the later part of study in 12 patients. Non-responders were counselled for definitive surgery. If unwilling, dose of progesterone was increased in a stepwise fashion (from 160 to 320 mg). In patients not desirous of fertility were advised to continue with LNG-IUD or low dose progestins (megestrol acetate) for an indefinite period with regular monitoring and follow up as long as there was no recurrence or progression of disease.

Data such as age, associated PCOS, grade and stage of tumor, response, pregnancy outcomes, oncology outcomes were observed and analysed. This is an observational study which will guide in future management of such complex situations which needs to be addressed diligently in the near future till more such studies are established. Simple methods such as percentages and proportion in excel were used to calculate the results and conclude.

The outcomes were classified as either oncologic or obstetric. The oncologic outcomes were assessed as complete response. Complete response is defined as no residual disease; partial response is defined as regression to EIN from EEC; stable disease is defined as no regression after treatment; progressive disease is defined as progression to EC from EIN or a grade or stage increase of EC; and recurrent disease is defined as the recurrence of the disease after complete response to therapy.

The obstetric outcomes included pregnancy rates.

RESULTS

A total of 17 cases who met the inclusion criteria were studied and analysed. The patients belonged to the age

group of 26- 35 years and 13/17 patients had PCOS (Tables 1 and 2).

Table 1: Age distribution.

Age in years	N=17	%
20-25	0	-
25-30	9	52.94
30-35	8	47.06
36-40	0	-

Most cases were seen in the age group of 25-30 years

Table 2: Associated PCOS.

PCOS	N=17	%
Yes	13	76.47
No	4	23.53

Majority of cases were found to have associated PCOS

There were 15 cases of EC–grade 1 and two cases of endometrial hyperplasia with atypia at the start of study diagnosed on endometrial biopsy (Figures 1-3). Thirteen cases had no myometrial invasion and two cases had myometrial invasion (deep in one). Treatment given was as mentioned in methods and methodology section (Tables 3 and 4).

Table 3: Diagnosis at start of study and grade in case of endometrial carcinoma.

Diagn-osis	N=17	%	Grade 1	Grade 2	Polyp
EH-ATY	2	11.76	-		1
EC	15	88.24	15		3

Majority (15 cases) with endometrial carcinoma had grade 1, endometroid type carcinoma. Four cases with above pathology were arising from endometrial polyps

Table 4: FIGO stage (1988) at diagnosis in endometrial carcinoma cases.

Stage	N=15	%
1A	14	93.33
1B	1	6.67

Majority had stage 1A cancer with one exception. One among stage 1A had superficial myometrial invasion as per FIGO -1988 surgical staging

Oncological and obstetric outcome

Complete response was seen in 13 patients (76.47%), one patient showed no response and three had progressive disease (17.65%) with 2 arising of polyps. Interestingly two of these cases showing complete response had myometrial invasion on MRI at the time of diagnosis. Three cases of progressive disease underwent definitive surgery followed by chemotherapy; and targeted therapy (rucaparib) in one case. Of the 3 cases of progressive two progressed to grade 3 carcinoma of which one had omental and aortic metastasis, one progressed to carcino-sarcoma with ovarian metastasis. One non-responder eventually had definitive surgical management (Table 5).

Table 5: Response to treatment.

Response	N=17	%
Complete	13	76.47
No response	1	5.88
Progressive	3	17.65

Almost 76.47% showed complete response to hormonal therapy with 3 showing progressive disease

Seven out of 13 patients with complete response had IVF which failed in all (2 are planned for IVF again). One conceived after intrauterine insemination and two naturally (one after failed IVF) (Table 6). Pregnancy was achieved in 3 patients (23.07%) with complete response.

Table 6: Obstetric outcome.

Outcome at first attempt	N=17	%
Natural conception	1	5.88
IUI	1	5.88
IVF success	0	-
IVF failure	7	41.18
Did not attempt pregnancy	8	47.06

7 of them failed IVF of which one failed twice who is planned for IVF again. One case conceived naturally after first failed IVF attempt. One patient who failed IVF first attempt is planning IVF again

On follow up, 5 patients out of 13 (13.46%) who had complete response initially had recurrence after 1-2 years out of which 2 underwent hysterectomy and 3 had re-challenge with progestins with remission again (Table 7). One of them actually recurred after 2 years post child birth. Eight patients (61.54%) with complete response are doing well in the follow up period extending over a period of 1 to 6 years from the time of inclusion into study period respectively.

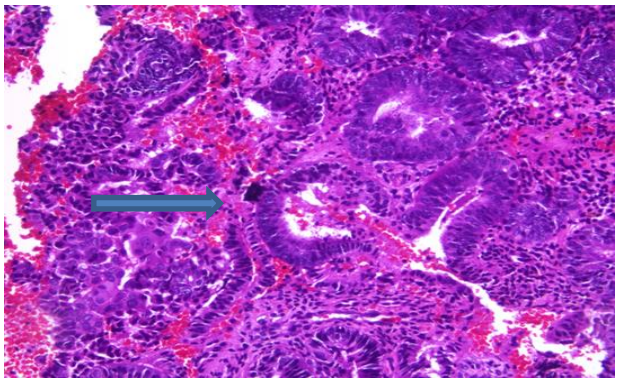

Figure 1: Atypical endometrial glands.

Closely placed glands lined by epithelium with mild to moderate dysplasia

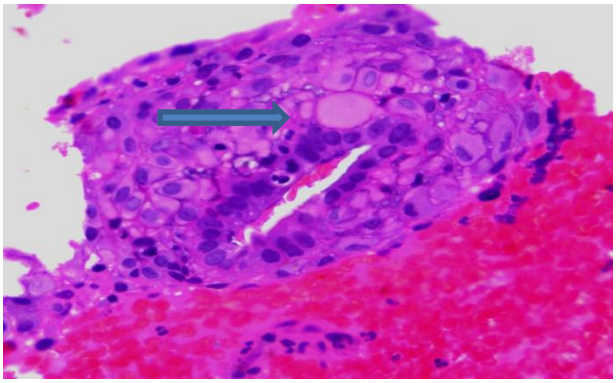

Figure 2: Endometrial gland surrounded by stroma with progesterone effect H & E magnification 10x.

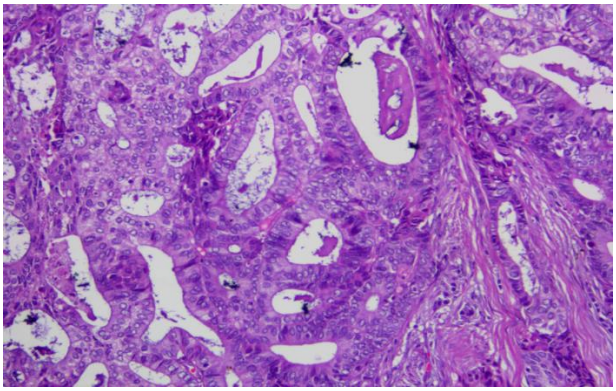

Figure 3: Adenocarcinoma-grade 1-H & E-magnification 10x.

Back-to-back arrangement of glands lined by pleomorphic epithelium

Table 7: Oncological outcome among patients showing complete response initially.

Outcome	N=13	%
Recurrence after 1 year	3	23.08
Recurrence after 2 years	2	15.38
Normal	8	61.54

Overall recurrence rate of 38.46% after 1-2 years was noted in cases showing complete to progestins initially

DISCUSSION

The management of young women with EC and atypical hyperplasia varies among clinicians. The standard initial treatment for EC includes total hysterectomy and bilateral salpingo-oophorectomy (BSO) and/or pelvic and para-aortic lymph node assessment.[5,8-10] Conservative treatment consists of medical management with hormonal therapy – mainly progestins as majority of the type I tumors respond to progestins. A retrospective meta-analysis of 28 studies showed 76% response with 26% recurrence at median of 19 months.[13] However, the optimal treatment is still debated. Operative hysteroscopy should be the preferred endometrial sampling method as co-existing endometrial polyps and bulky growths can be excised at the same time and its association with a higher remission rate.[14] In the present study 2 cases with endometrial polyps showed complete response probably due to complete excision at the time of endometrial sampling.

In our study we found a complete response to oral progestins along with LNG-IUD (available as Mirena) in majority of the cases. During the earlier part of the study, when Mirena was not used many patients required escalation of the dose of megestrol acetate from 160 mg up to 320 mg. A study by Fann et al found similar results with oral progestins and LNG-IUD.[15] Oral progesterone is the first choice of conservative treatment, but it is prone to bring about adverse reactions such as nausea and vomiting, weight gain, and liver function damage after being taken at a large dose orally, and it causes poor compliance of patients. LNG-IUS can enhance the concentration of levonorgestrel in local tissues in the uterus to be much higher than the blood concentration, thereby reducing the need for higher dosages of oral progestins significantly reducing the systemic adverse reactions.[16] LNG-IUD along with oral progestins might be useful in optimising the dose of oral progestins without the need for further escalation of dosage. It was our observation that some of the patients responding to conservative management resulting in thinned out endometrium still showed some atypia with decidualisation. This could represent hormonal/LNG-IUD effect and should be discerned from true atypia with endometrial hyperplasia.

Pregnancy rate described in literature for exclusively hormonal treatment is between 35-60%. The present study showed a pregnancy rate of 23.07% after showing complete response to progestins. There were three patients with disease progression and one non responder in the current study at four to 66 months duration of follow up. Five of 13 patients (38.46%) who had complete response on initial treatment recurred later and were offered re-treatment with progestins which again induced remission. Therefore, it appears that these patients can be offered a re-treatment with progestins. Even if conservative treatment is initially successful with biopsy-proven regression of disease about 40% of the responders will recur, even despite the use of maintenance therapy.[17,18] Cumulative data suggest that ART is associated with a higher live birth rate compared with spontaneous conception in young women with EC.[19] Lower spontaneous fertility rates could reflect the presence of EC risk factors that are also associated with infertility, such as obesity, PCOS, and chronic anovulation. In a recent systematic review, the live birth rate among women who underwent ART was significantly higher than the rate among the remaining women who were presumed to have attempted pregnancy spontaneously (39.4% versus 14.9%, respectively; p=0.001).[17] Interestingly in the present study 2 cases conceived naturally and one conceived after intra uterine insemination.

Three of our patients had disease progression with higher grade of tumour on repeat biopsy indicating the importance of molecular subtyping of all endometrial biopsy samples at the time of initial diagnosis to remove

or decrease subjective errors. Nearly 5% of grade 1-2 tumours have p53 mutation and are not suitable for conservative treatment. The ProMisE molecular classifier can be applied to endometrial biopsy, demonstrating high concordance with final hysterectomy in this series K=0.87, consistent with the literature. It uses pragmatic molecular tests to identify ECs with mismatch repair deficiency (MMRd), mutations in the exonuclease domain of DNA polymerase epsilon (POLE), and wild type or aberrant p53 expression (p53 wt or p53 abn respectively).[20] MMR deficiency is associated with Lynch syndrome in 10% (as against 3% for all EC).

Some of the young women with EC may harbour BRCA mutation. A comprehensive germline mutation panel testing on blood sample may be advised selectively depending on the resources and in non-responders to hormonal treatment. This also helps us in optimal management of patients in case of recurrence with targeted therapy as seen in one of our patients with germline BRCA mutation who developed liver metastases and still had good response to PARP inhibitor rucaparib given orally.

The major limitations of our study were its retrospective nature and lack of molecular pathology study of endometrial biopsy. Larger sample size will be required to add to the current evidence.

CONCLUSION

Hormonal therapy is very effective in the management of early ECs – if conservation is desired. LNG-IUD along with oral progestin is an effective combination as it might be useful in optimising the dose of oral progestins without the need for further escalation of dosage. LNG-IUD or low dose progestins alone can be used for maintenance to prevent recurrence if conception not immediately desired after complete remission.

PCOS appears to be a common risk factor among majority of patients. Conception rates are low even after reversal of the malignancy. ART should be preferably tried after 6-9 months of complete response to avoid delay as there is a risk of recurrence. Hysterectomy should be advised – if hormonal treatment fails and after completion of childbearing. In case of recurrence re challenge with progestins can be tried in those not willing for definitive surgery. Myometrial invasion may not absolute contraindication for fertility sparing treatment. The guidance for managing conservatively young patients with endometrial carcinoma can never be fixed and hence individual approach for care and management for each patient as per different characteristics and individual expectations.

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