A review of the fertility sparing approach to endometrial cancer: current recommendations

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Endometrial cancer is the most common cancer of the female genital tract; with 20%-25% diagnosed pre-menopausally, the median age in this group of patients is 40 yrs (range 31-45 yrs) (1). However future fertility is an issue for these young patients as many as 61%-79% are nulliparous compared to 24% in the older group (1). In women with early stage endometrial cancer the standard surgical treatment of total hysterectomy, bilateral salpingo-oophorectomy (TAHBSO) and possible lymph node assessment is often not acceptable. The conservative fertility retaining option is often only possible in a select group of early stage cases, and in these cases the risks are something that needs to be carefully weighed.

The low risk group of grade 1 endometrioid adenocarcinoma confined to the endometrium without lymphovascular space invasion (LVSI) or disease outside the uterus are those who may be candidates for conservative treatment. Since these patients do not undergo the usual surgical staging procedure they need to be carefully evaluated. Indeed as survival in these group approaches 95% and above it can be difficult to contemplate the risk associated option of conservative management. However it is not uncommon for women to come to clinic and request this line of management.

It is important that several factors are assessed before contemplating the conservative option. Pre-treatment investigation must include a hysteroscopy and biopsy and contrast MRI. The biopsy will give information regarding cell type i.e. endometrioid adenocarcinoma, grade 1 and may exclude the presence of LVSI and may also detect myometrial invasion. The contrast-enhanced MRI is used to assess the primary tumour and exclude myometrial invasion. In addition it can be used to exclude cervical or extra uterine disease including lymph nodal involvement. This group of patients with grade 1 cancer and no myometrial invasion (i.e. presumed IA) will have a risk of lymph nodal disease of approximately 3%-5% (2). Some clinicians have advocated a laparoscopy with concurrent peritoneal washings and a preoperative CA125. Others recommend a PET scan for evaluation at distant sites but microscopic disease will not be detected. The continual evaluation of the sentinel node procedure may be relevant in these early cases to evaluate and exclude lymph node involvement. Finally, the case should be evaluated in a multi-disciplinary team setting, the options discussed and a treatment plan reached (see Table 1 for prerequisites). All other cases other than grade 1, endometrioid adenocarcinoma without apparent LVSI, myometrial, cervical or extrauterine disease should be offered standard treatment involving surgery including TAH BSO, pertioneal washes and possibly lymph nodal harvest (pelvic with/without para-aortic nodes).

Table 1. Pre-treatment factors that need to be met prior to conservative management

- Age less than 45 years and wishes fertility, understands consent implications
- Grade 1 endometrioid carcinoma
- No LVSI
- MRI: no myometrial invasion
- No evidence of
  - Cervical involvement,
  - Ovarian involvement,
  - Lymph nodal involvement, or
  - Other extra-uterine disease
- MDM confirmed G1 (2 gynoncology pathologists review)
- stage IA confined to endometrium

THE OPTIONS FOR CONSERVATIVE MANAGEMENT

The options are essentially three fold. Firstly in those deemed appropriate (ie stage IA as above, grade 1) to keep the uterus and ovaries and treat with hormonal medication. The other option is to have curative surgery, including TAHBSO but with assisted reproduction techniques (ART) before with surrogacy after surgical treatment. The third option is to have hysterectomy with ovarian conservation and consider ART before or after again with surrogacy. Clearly in the latter option of ovarian conservation there is a risk with the ovaries.

There is also evidence that ovarian secondary disease occurs at an increased rate in younger patients (14%-25% for under 45 yrs versus 5% overall for those greater than 45yrs). But a large study from the Korean GOG (3) demonstrated no difference in the recurrence rate or 5 years if the ovaries were retained versus those without ovaries. They concluded that if the ovaries were grossly normal and there was no extrauterine disease, the risk was less than 1%. If however the ovary looks abnormal then it needs to be assessed; if it does contain disease then it is not advisable to treat conservatively as lymph nodal disease within the group with isolated ovarian involvement can be as high as 32% and the five year survival is reduced in this group to 72.2% (2).

There is also the condition of synchronous primaries with respect to ovarian and endometrial cancer. In the group of patients presenting with ovarian cancer up to 10% will have a synchronous endometrial cancer whilst in the group presenting with endometrial cancer as many as 5% may have a synchronous ovarian primary malignancy. Features associated with these synchronous primaries include ovarian endometriosis, atypical endometrial hyperplasia, low grade histologies in both sites and a unilateral ovarian tumour.

TREATMENT OPTIONS AND RISKS

The majority of treatment strategies have focused on hormonal treatment with conservation of the full reproductive tract. Progestins have been the may stay of treatment in these cases. Progesterone stimulates histological differentiation from glandular to secretory structures and inhibits the estrogenic effect and suppresses cell proliferation. The most commonly used treatment is medroxyprogesterone acetate at doses of 200-800 mg daily, used in 50%-57% (2). Megestrol is used in 23%-24% of cases at 10-40 mg per day. The summary of the published literature concerning complex atypical hyperplasia (CAH) and endometrial cancer (ECa) is listed in Tables 2 and 3 respectively.

If one deals with CAH the 100 patient grid is a good tool for discussion when it comes to explaining the options in the clinic setting with the patient. (see Figure 1 which illustrates the case with CAH). Essentially 86% will have an initial response resulting in a complete response (CR) in 75%. In the group with a CR 50% will have a lasting CR and 25% of the original cohort will recur. Considering the 100 group of patients therefore 14% will have no response, 11% a transitory response and 25% will recur.

The overall response rates to progestins first line in patients with grade 1 confined to the endometrium is 75% over a median time of 3 months, and median treatment duration of 6 months. (1, 2, 4-6). The relapse rate approaches 25% with a mean time to relapse of 5 months. In summary, the hormonal treatment studies in grade 1 endometrial cancer indicate that preservation of fertility with a complete response to hormone treatment can be achieved only in 50% (initially), a transitory response or progression is seen in 25%, and there is no response in 25% (1, 2, 4-6). The 100 patient grid for endometrial cancer stage I is illustrated in Figure 2. Essentially 75% will have an initial response resulting in a CR in 50%. In the group with a CR 20% will have a lasting CR and 30% of the original cohort will recur. Considering the 100 group of patients therefore 25% will have no response, 25% a transitory response and 30% will recur. This illustrates that 80% of patients will need definitive surgical treatment at some point in the patients disease course. In summary therefore the response to the standard hormonal treatment in endometrial cancer with preservation of fertility and a CR is 20%; a temporary response is seen in 30% and no response or progression is seen in 50%.

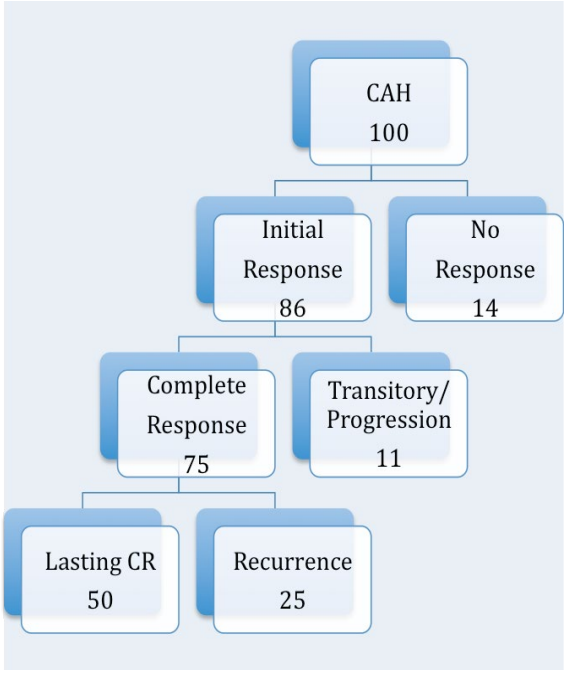

Figure 1. The 100 patient grid for CAH, outcome from hormonal treatment.

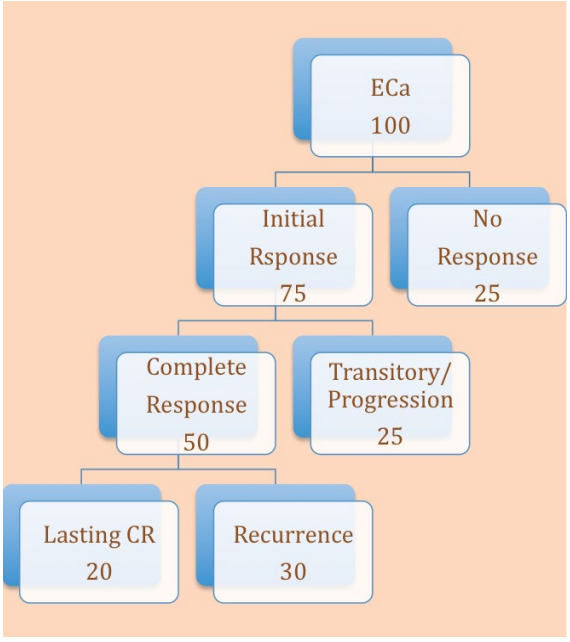

Figure 2. The 100 patient grid for endometrial cancer, outcome from hormonal treatment.

Table 2. Summary of the published studies of complex atypical hyperplasia (CAH), treatment and obstetric outcome from 2004-2010.

Study Dates	No. studies	No. of women	No. with CAH (mean, range)	Treatment	Regression	Relapse	Number of subjects achieving pregnancy	Live births	Median follow up time (months)
2004-2010	16	215	111 (13, 1-45)	MPA, megestrollUD	73	26	24/68	28	6-98

Table 3. Summary of the published studies of endometrial cancer (ECa), treatment and obstetric outcome from 2001-2014.

Study Dates	No. studies	No. with ECa (mean, range)	Treatment used	Regression	Relapse	Number of subjects achieving pregnancy	Live births	Median follow up time (months)
2001-2014	48	465 (10, 1-81)	MPA, megestrollUD Norethisterone Hydroxy progesterone acetate	252	107	86/280	89/280	6-120

Table 4. The published data concerning risk of disease progression and potential death in conservatively managed endometrial cancer cases.

Case No.	Age	Initial Response	Pregnancy	Relapse Months	Site
1	31	Yes	No	36	Peritoneal carcinomatosis
2	34	Yes	No	20	Ovarian metastases
3	30	Yes	Yes	8 after delivery	Peritoneal carcinomatosis
4	40	Yes	No	24	NA
5	NR	Yes	No	24	Peritoneal carcinomatosis
6	31	Yes	No	36	First uterus Second lung

NA= Not available, NR= not reported

Adapted from Chiva & Alonso 2011 *Eur Obstet Gynecol* (2)

Other treatments have been used, with reports of the Mirena IUCD being used but there are recurrences in this group (2). The Mirena has been used with gonadotrophin releasing hormone analogues to treat both endometrial hyperplasia and cancer with complete response rates of 95% and 57.1% respectively, with recurrence in the latter of 14.3% and progression rates of 28.6% (2). In addition, aromatase inhibitors have been recommended for obese patients. Tamoxifen given with progestins can result in down regulation of hormonal receptors more than progestins alone (2).

It is difficult to draw any consensus regarding follow up from all the studies. As the median response time is 3 months it has been proposed that repeat endometrial biopsies by hysteroscopy should be performed every three months. This should be until there is a complete response or a pregnancy. If however there is no response after six months then most clinicians advocate standard surgical treatment. Once a CR has been achieved then intermittent biopsies (in the pre-ovulatory phase) should be taken every 3 to 4 months.

There is limited data concerning the response rates to progestins in the recurrent disease setting in patients with grade1 confined to the endometrium (5,7-9). In relapsed disease approximately 40% re-challenge with progestins and the CR ranged from 72%-86%. In the Ramirez (5) and Yahata (7) studies 21 patients out of 26 underwent hysterectomy with 16 of the 21 having residual cancer (15 grade 1), all were alive and well over the study period.

However, a word of caution needs to be discussed with patients and that is the risk of disease progression and potential death. There is limited data in the literature concerning this but Chiva & Alonso (2) reported 6 deaths in those treated conservatively and the details are outlined in Table 4 .

A protocol for treatment can therefore be advocated which is illustrated in Figure 3.

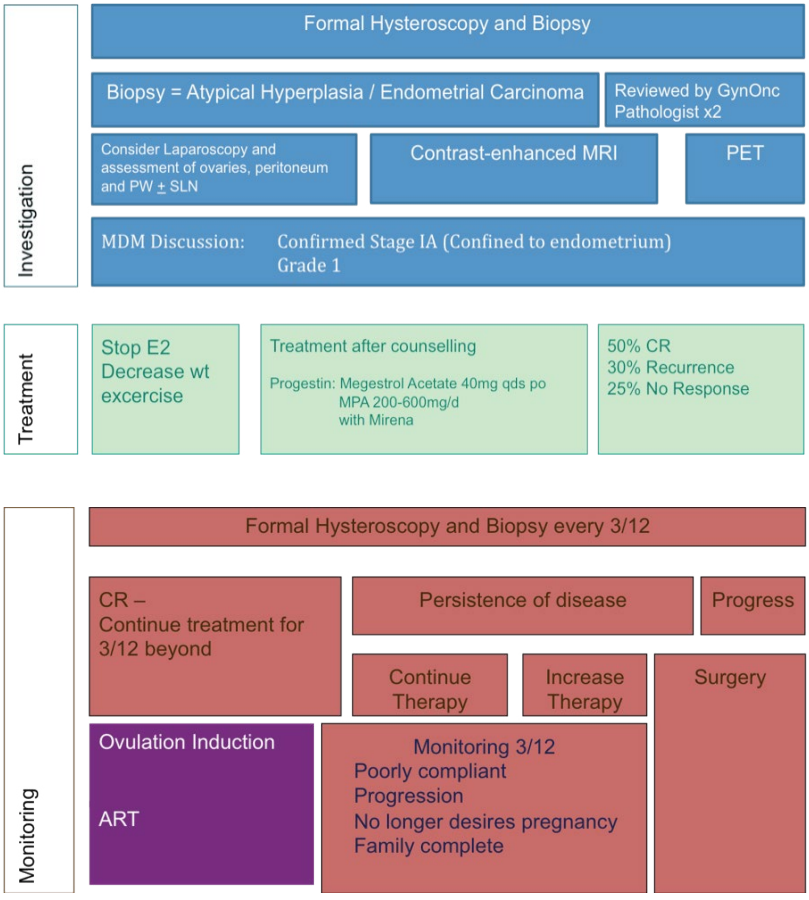

Figure 3 Protocol for the conservative management of endometrial cancer in patients wishing to retain fertility

REPRODUCTIVE OUTCOME

The reproductive outcome is variable in these patients with a pregnancy rate of 35%-40% (1,2,4-6). It has to be stressed to patients that not all conservatively treated patients have a pregnancy because in many cases the cause of the endometrial cancer is linked to the infertility via a hormonal disorder. A large publication variation on the need of assisted reproduction techniques (ART) has been seen varying from 17.9% to 66% (1-5). In the Ramirez paper there were pregnancies in 20 patients, although it is not reported how many attempted pregnancy, with 12/20 (60%) using ART and 31 births in 16 patients (5).

Ichinose et al. (10) examined the issue of whether fertility treatment increases recurrence risk. In their study of 36 patients (23 endometrial cancers and 13 CAH), 18 of the 26 wanting to get pregnant underwent infertility treatment and conceived; with a live birth rate of 61.5% in 12.2 months, of the 21 undergoing ART 13 had a live birth. They divided the 36 patients into three groups: (a) those having infertility treatment and had a live birth 16 (ECa:CAH 10:6);(b) those having infertility treatment and no live birth 10 (ECa:CAH 6:4); (c) those not having any infertility treatment 10 (ECa:CAH 7:3). The duration of the treatment requiring a CR was not different between the groups 16 months, 16 months and 10 months respectively. Interestingly, rate of recurrence was the lowest in group (a) (having infertility treatment and a pregnancy) 3 (18.8%) versus 7 (70%) for the other two groups.

There are several options available to the patient if the conservative non-surgical option is not appropriate. Prior to surgery one can undergo IVF and embryo cryopreservation; ovarian stimulation and oocyte retrieval and

storage (if a partner is not present) or ovarian tissue harvest and storage. Surgery could allow for ovarian conservation (risks previously explained) with or without transposition followed by ovarian stimulation if not embarked prior to surgery and then the necessary adjuvant treatment. Pregnancy would require a surrogate carrier. Information regarding outcome in these cases are limited to case reports.

CONCLUSION

The conservative treatment option in early stage G1 is a valid option if childbearing is not complete. However there needs to be strict selection (G1 No MI, No LVSI, no extra-uterine disease). The biopsy needs to be reviewed by 2 gynaecological oncology pathologists within a multidisciplinary meeting setting. Surveillance of the ovaries is necessary to reduce the risk of concomitant malignancy. The risks and the benefits need to be carefully explored and implications discussed. Fertility is not guaranteed and up to 80% need surgical treatment. There is an inherent reduced fertility of those treated with a significant number needing ART (18%-60%). Finally, it must be understood that there are risks from the conservative treatment with deaths having been reported despite a good outcome in the majority with successful pregnancies; and many women having had the risks explained will still wish to proceed with a conservative approach.

Conflict of interest

We declare no conflicts of interest.

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