Fertility preserving options in Endometrial cancer

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Second most common gynaecological cancer worldwide

- 4% are < 40 years of age, many of whom still wish to retain their fertility

- Nulliparity seen in 50% patients <45 years of age and 70% females < 40 yrs
Patient characteristics in carcinoma before 45 years

- Younger patients generally have lower stage and grade
- Endometroid carcinoma is the most common type
- Synchronous ovarian malignancy is seen in 5% of cases
- Risk of lymph nodes metastasis is negligible with no myometrial invasion and 3% with inner 3rd invasion
Fertility preservation

- Standard approach for management is Hysterectomy
- Conservative treatment with hormones can be considered in females less than 40 who are strongly desirous of child bearing
- Appropriate Consent and counselling: non standard treatment, pros and cons, success rates, risk of progression, side effects, follow up protocols, response rates.
- Relapse risk, use of ART and also pregnancy rates must be discussed
Work up for fertility preserving therapy

- Teamwork of gynec-oncologists, fertility specialists, psychosocial experts
- Patient must be referred to a specialized center
- D and C with or without hysteroscopy must be performed
- Patients with well-diff endometroid tumors can only be considered
- Histopathology must be confirmed by a specialist Gyne-oncopathologist
- CEMRI of Pelvic should be performed to exclude overt myometrial invasion and adnexal involvement.
- Laparoscopic staging/ evaluation of adnexa (optional)
Optimal indications for fertility sparing progestin therapy

- Histologically confirmed endometroid adenocarcinoma Grade 1 (well diff)
- Disease confined to endometrium
- No evidence of myometrial invasion on imaging
- No evidence of extra uterine spread
- Strong desire to preserve fertility
- Age <= 40 years (relative indication)
- No contra indication for medical treatment
- Informed consent
Molecular markers/ Hormone receptors

- Help in predicting response
- Estrogen – progesterone receptor status
- Routine check is not recommended since 50% of PgR-negative patients will respond to treatment
- PTEN gene and phospho-AKT expression are associated with good response to progestogen therapy.
- MLH1 gene in tissues with CAH are associated with treatment failure and a high risk of progression to endometrial carcinoma
Management

- PROGESTOGENS is the main stay of treatment
- Act on Progesterone alpha & beta receptors
  - alpha receptors: cell senescence, apoptosis, cell cycle inhibition
  - Beta receptors: secretory differentiation, cell growth inhibition
- Act by downregulation of estrogen receptors, activating enzymes in estrogen metabolism and cell cycle regulation
- Progestin is known to enhance p27 expression, resulting in inhibition of cyclin E-Cdk2 function and suppression of the cell cycle
Hormone Therapy: Progestins

- Oral high dose progestins
  - Megesterol acetate (Megace/Endace)
  - Medroxyprogesterone acetate
- LNG-IUD only
- LNG-IUD+ GnRH analogues
- Hysteroscopic resection with progestogen therapy
Oral high dose progestins

- Mainstay of treatment
  - Medroxyprogesterone acetate (MPA; 400–600 mg/day)
  - Megestrol acetate (MA; 160–320 mg/day)
- Continuous daily dosage
- The complete response (CR) rate is 70%–80% in EEC and EAH patients after a median treatment period of 6–9 months using MPA or MA.
- Potency reported to be similar. Complete response rates are same
- Side effects include vaginal bleeding, weight gain, thromboembolism, mood and libido changes, headaches, breast tenderness, sleep disorders, and leg cramp
LNG-IUS

- Delivers a higher dose of progestin to the endometrium avoiding systemic complications
- Better patient’s compliance:
  “one-time insertion and long-term protection”. No pill everyday
- Prevents disease recurrence after CR due to persistent release of progestin
- Should be used carefully in patients with enlarged uterine cavity (as sufficient dose may not reach endometrium)
- Pooled complete response rate is 46% (95% CI 29%–63%) according to meta-analysis. 
  Baker J et al Gynecol Oncol 2012
- Hence it has been recommended to be used with GnRH analogues. Around 85% CR have been reported with combined. Kim et al
HYSTEROSCOPIC RESECTION + PROGESTOGEN THERAPY

- An innovative method: hysteroscopic resection of the endometrial tumour along with the myometrium underlying the tumour followed by oral megesterol acetate 160 mg a day.

- Recommended with small discrete lesions evident on hysteroscopy.

- The possible complications of hysteroscopic dissemination of disease, post-op intrauterine adhesions and pregnancy complications

- Prospective study of 25 patients showed a CR of (89.3%) (median time to CR 3 months). More than half of the responders (57.7%) attempted to conceive with 93.3% and 86.6% pregnancy and live birth rates, respectively. *Falcone F et al J Gynecol Oncol* 2017
In order to assess response, D&C, hysteroscopy and imaging at 3-6 months must be performed.

If no response is achieved after 6 months, standard surgical treatment should be performed.

Response rates associated with the conservative management of endometrial carcinoma are around 75%.

Pronin et al., 2015; Park & Nam, 2015
Relapse Rates

► Although the initial response rate promising, the recurrence rate is high.

► Reported pooled recurrence rate is around 40%.
  

► Close surveillance is therefore mandatory after achieving a complete response to progestin treatment.

► Definitive surgery is necessary in view of high recurrence rates.
Subsequent disease progression is extremely rare even in patients who did not respond.

In the literature, only 10 patients with stage II or higher disease after fertility-sparing therapy have been reported, 4 of whom died of disease. However, it is not clear whether these cases had true early endometrial cancer at their initial diagnosis and whether fertility-sparing therapy compromised their survival. (Gallo ID, et al. Am J Obstet Gynecol 2012)

Almost all recurrences are well-differentiated tumors and confined to the endometrium and thus amenable to surgery.
Follow up

- If the patients wish to conceive after achieving a CR, pregnancy trials can be attempted immediately.
- Maintenance treatment should be considered in responders who wish to delay pregnancy.
- A prophylactic hysterectomy should be recommended after the completion of family planning because of a high reported rate of disease recurrence.
- The safety of alternative strategies such as the delay of hysterectomy until recurrence has not yet been evaluated.
Pregnancy after treatment


- 40% of patients who respond successfully, conceive; half of them using ART. Kalogiannidis & Agorastos, 2011

- Pooled live birth rate is 28%, and reached 39% when assisted reproduction technology is used. Koskas M, et al. Fert Steril. 2014
The ovaries can be preserved in women younger than 45 after a thorough preoperative evaluation (ruling out ovarian mets/synchronous ovarian cancer) and extensive intraoperative exploration.

Ovarian preservation apparently had no effect on overall survival and the findings were validated by meta-analysis (Sun et al., 2013).

The National Cancer Data-base search (Wright et al. 2016):
- 15,648 women <50 years who underwent surgery for stage I endometrioid adenoca
- 1,121 (7.2%) who had ovarian preservation
- 14,527 (92.8%) who underwent oophorectomy.

Ovarian sparing/preservation was not independently associated with survival.

Thus ovarian preservation can be safely considered in young patients.
Fertility preservation is generally not recommended for anything more than Grade 1 (limited to endometrium).

Evidence in patients with superficial myometrial invasion and/or grade 2–3 disease is limited.

Table 2. Published studies showing the efficacy of progestin therapy in endometrial cancer with myometrial invasion and/or grade 2–3 differentiation

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of cases</th>
<th>Progestin therapy</th>
<th>Complete response, n (%)</th>
<th>Recurrence, n (%)</th>
<th>Follow-up time, median or range, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sardi et al.</td>
<td>1998</td>
<td>1</td>
<td>MPA (50 mg/day)</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Zuckerman et al.</td>
<td>1998</td>
<td>1</td>
<td>MPA</td>
<td>1 (100)</td>
<td>0</td>
<td>Not reported</td>
</tr>
<tr>
<td>Imai et al.</td>
<td>2001</td>
<td>2</td>
<td>MPA (600 mg/day)</td>
<td>1 (50)</td>
<td>1 (100)</td>
<td>7–47</td>
</tr>
<tr>
<td>Kaku et al.</td>
<td>2001</td>
<td>2</td>
<td>MPA (600 or 800 mg/day)</td>
<td>1 (50)</td>
<td>0</td>
<td>19–22</td>
</tr>
<tr>
<td>Gotlieb et al.</td>
<td>2003</td>
<td>3</td>
<td>MPA (200 or 600 mg/day) or MA (160 mg/day)</td>
<td>3 (100)</td>
<td>1 (33)</td>
<td>16–94</td>
</tr>
<tr>
<td>Koskas et al.</td>
<td>2011</td>
<td>3</td>
<td>NES (20 mg/day), MA (160 mg/day), or NG (5 mg/day)</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>12–60</td>
</tr>
<tr>
<td>Brown et al.</td>
<td>2012</td>
<td>1</td>
<td>LNG-IUD</td>
<td>1 (100)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Park et al.</td>
<td>2013</td>
<td>48</td>
<td>MPA (80–1,000 mg/day) or MA (40–240 mg/day)</td>
<td>37 (77)</td>
<td>16 (43)</td>
<td>48</td>
</tr>
</tbody>
</table>
Park et al. in their study of 48 patients reported the oncologic and reproductive outcomes in patients with superficial myometrial invasion and/or grade 2–3 disease.

The complete response rates to progestin therapy in that study were:
- 76.5%, in patients with superficial myometrial invasion
- 73.9%, with grade 2 stage IA (without myometrial invasion)
- 87.5%, grade 3 stage IA (without myometrial invasion)

The recurrence rates after progestin therapy in that study were 23.1%, 47.1%, and 71.4%, respectively, with no evidence of disease progression after fertility-sparing progestin therapy.

Fertility-sparing progestin therapy is a viable in these patients. Further studies are needed.
Future: Molecular classification impact on decision making

- Based on TCGA classification, integrated genomic characterization of endometrial carcinoma has been proposed.
Future: Molecular classification impact on decision making

- The prognostic value of molecular classification is independent of stage.
- This classification refines the prognosis of grade 3 cancers (not a homogenous high risk cohort).
- Classification would help better define patients in whom fertility preservation is considered.
- Would be specially advantageous for patients with grade 2/grade 3 disease, desirous of preserving fertility.
FUTURE HORMONAL TREATMENT

- Bazedoxifene inhibits the effects of conjugated estrogens on endometrium.
- TSEC (Tissue selective estrogen complexes): antiproliferative action
- Onapristone: PR antagonist
- Endoxifen: Active metabolite of Tamoxifen
- Histone deacetylase inhibitor: induces upregulation of PR messenger (m)RNA.
Take home points....

- **For Fertility preservation** team of Gynecologist, Oncologist, Fertility specialist to be involved in treatment planning
- Oral high dose progesterone are the treatment of choice in carefully selected patients
- Treatment to be monitored closely with 3-6 monthly monthly TVS & Endometrial sampling
- Pregnancy should be achieved as soon as possible preferably with ART
- Relapse rates are high, definitive surgery needs to be planned as soon as childbearing is complete
....WITH A BABY OR WITHOUT, YOU ARE VALUABLE....AND YOU MATTER