Fertility preserving options in Endometrial cancer

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Endometrial cancer

- 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 gyne-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 adenoca 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*

MONITORING AFTER CONSERVATIVE MANAGEMENT

- 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%.
  Gallos ID et al. Am J Obstet Gynecol. 2012 ; Park JY, Kim DY, Kim JH, et al. Eur J Cancer. 2013
- Average time to response is 3 to 9 months and the majority will have long term response . *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%

Gallos ID, et al. Am J Obstet Gynecol 2012

- Close surveillance is therefore mandatory after achieving a complete response to progestin treatment.
- Definitive surgery is necessary in view of high recurrence rates

Safety

- 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. *Gallos 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

- ART treatment soon after achieving tumor remission improves pregnancy and live birth rates Carneirol MM et al JBRA Assist Repro 2016
- 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*

Ovarian preservation role

- The ovaries can be preserved in women younger then 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.*

Advanced stage

- 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

Author	Year	Number of cases	Progestin therapy	Complete response, *n* (%)	Recurrence, *n* (%)	Follow-up time, median or range, months
Sardi et al. [103]	1998	1	MPA (50 mg/day)	0	0	20
Zuckerman et al. [104]	1998	1	MPA	1 (100)	0	Not reported
Imai et al. [105]	2001	2	MPA (600 mg/day)	1 (50)	1 (100)	7–47
Kaku et al. [51]	2001	2	MPA (600 or 800 mg/day)	1 (50)	0	19–22
Gotlieb et al. [19]	2003	3	MPA (200 or 600 mg/day) or MA (160 mg/day)	3 (100)	1 (33)	16–94
Koskas et al. [106]	2011	3	NES (20 mg/day), MA (160 mg/day), or NG (5 mg/day)	3 (100)	2 (67)	12–60
Brown et al. [107]	2012	1	LNG-IUD	1 (100)	0	13
Park et al. [12]	2013	48	MPA (80–1,000 mg/day) or MA (40–240 mg/day)	37 (77)	16 (43)	48

Advanced Stage

- 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

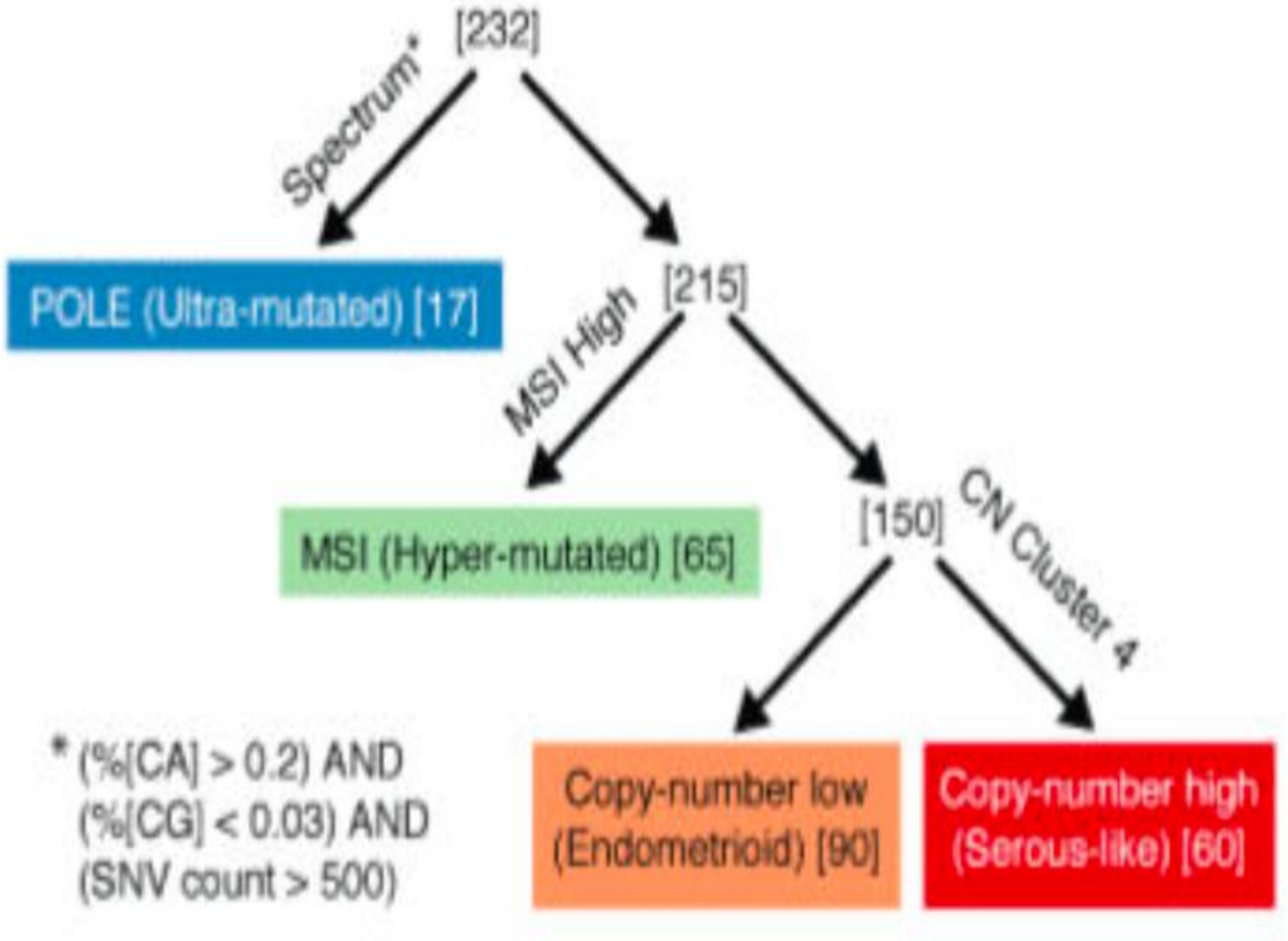
  76.5%, in patients with superficial myometrial invasion

  73.9%, with grade 2 stage IA (without myometrial invasion

  and 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

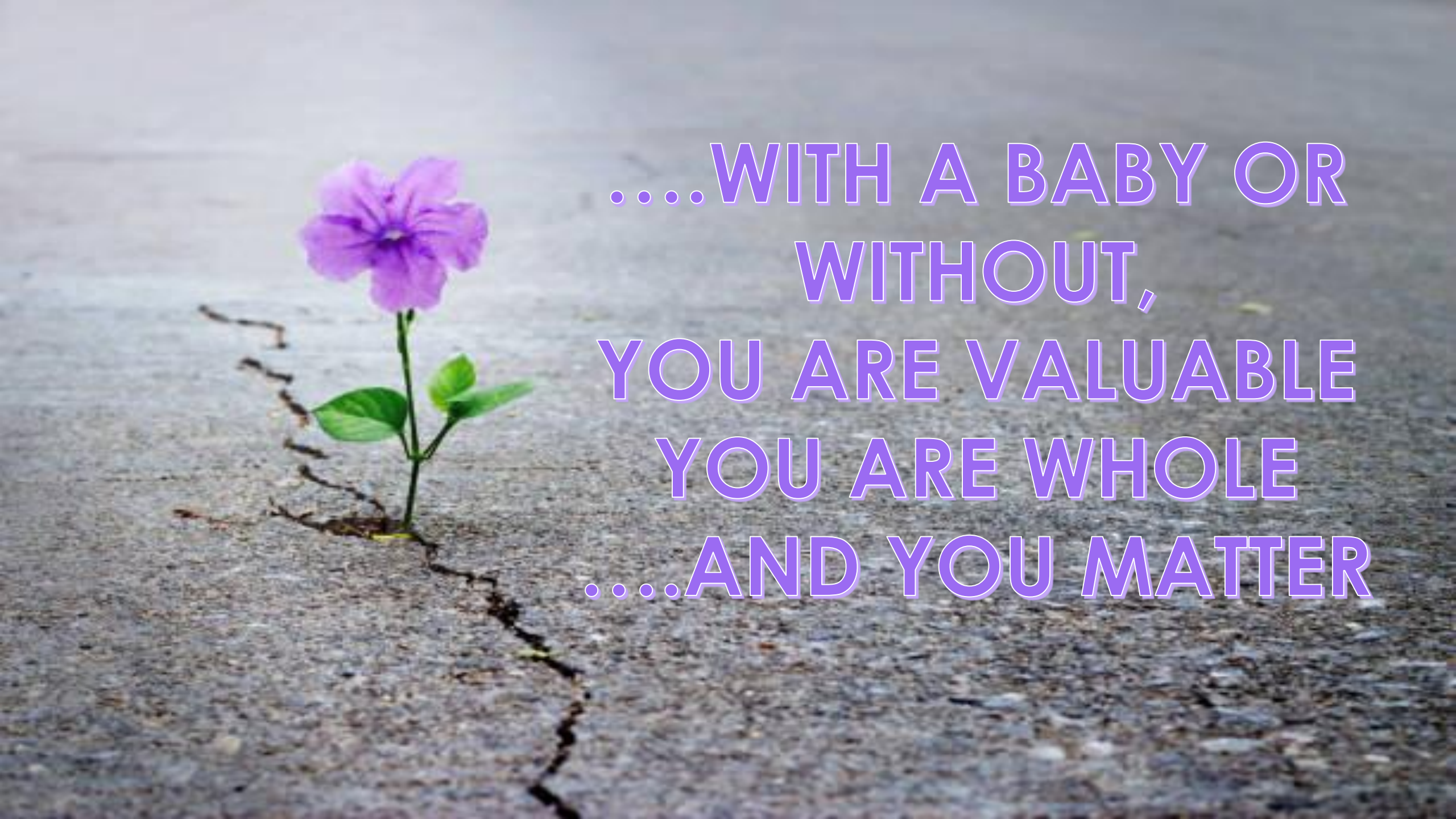
- The prognostic value of molecular classification is independent of stage
- This classification refines the prognosis of grade 3 cancers (not a homogenous high risk cohort)
- Classification would help better define patients in whom fertility preservation is considered.
- Would be specially advantageous 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
YOU ARE WHOLE
....AND YOU MATTER