Taylor & Francis
Taylor & Francis Group

The Journal of Obstetrics and Gynaecology

Journal of Obstetrics and Gynaecology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijog20

New insights into fertility-sparing treatment of endometrial cancer

Luca Giannella, Camilla Grelloni & Andrea Ciavattini

To cite this article: Luca Giannella, Camilla Grelloni & Andrea Ciavattini (2024) New insights into fertility-sparing treatment of endometrial cancer, Journal of Obstetrics and Gynaecology, 44:1, 2370747, DOI: 10.1080/01443615.2024.2370747

To link to this article: https://doi.org/10.1080/01443615.2024.2370747

Published online: 28 Jun 2024.

JOURNAL OF OBSTETRICS AND GYNAECOLOGY
2024, VOL. 44, NO. 1, 2370747
https://doi.org/10.1080/01443615.2024.2370747

Taylor & Francis
Taylor & Francis Group

EDITORIAL

New insights into fertility-sparing treatment of endometrial cancer

We thank the Editor-in-Chief of the *Journal of Obstetrics and Gynaecology*, Ayman Ewies, for the opportunity to discuss recent work dealing with a topic of great clinical interest that may encourage future research.

Ogunbiyi *et al*. (2024) recently published a systematic review and meta-analysis about oncological and reproductive outcomes in 624 women with stage 1aG1 endometrial cancer (EC) undergoing different fertility-sparing treatments (FST): oral progestin (OP), levonorgestrel intrauterine system (LNG-IUS), and combined therapy including hysteroscopic resection (HysR) followed by adjuvant hormonal therapy. The results showed an overall complete remission rate (CR) of 77% (95% CI: 70–84%), a relapse rate of 20% (95% CI: 13–27%), and a live birth rate of 20%. The HysR + hormonal adjuvant treatment showed the best oncological and fertility outcomes, with a CR of 84% (95% CI: 68–100%) and relapse rate of 9.3% (95% CI: 0.0–18%). This work provides further discussion points relating to the FST of endometrial cancer to better stratify the various risk classes and, therefore, improve their management.

EC is the most common gynecological cancer in developed countries, with 417,367 new cases worldwide in 2020 (Siegel *et al*. 2020). Approximately 4% of women diagnosed with EC are under age of 40 years, with a continuously growing incidence in this age group, probably due to the spread of risk factors such as obesity (Yang *et al*. 2023). Given that the mean age of women giving birth to their first child is gradually increasing, a non-negligible number of women who have not yet completed their families are diagnosed with EC every year (EUROSTAT, 2021).

Although the standard treatment of EC is represented by definitive surgery, patients willing to conceive should be referred to a specialised centre and optimally counselled by a multidisciplinary team about FST and the risk of i) under-staging of cancer, ii) progression/recurrence of disease, iii) lower reproductive potential, considering the state of the uterus after treatment, age, ovarian reserve and comorbidities (obesity, polycystic ovary, insulin resistance) (ESGO/ESHRE/ESGE 2023; Gullo *et al*. 2023).

The most recent ESGO/ESHRE/ESGE guidelines (2023) support FST after a careful patient selection, following strict inclusion criteria:

- Histopathological diagnosis confirmed by an experienced second opinion.
- Evidence of well-differentiated (grade 1, G1) endometrioid adenocarcinoma without myometrial invasion (stage 1a according to FIGO 2023 classification).
- Radiological examinations performed by a specialised operator (MRI or transvaginal ultrasound) confirming the cancer is confined to the endometrium.
- Exclusion of extrauterine disease or synchronous metastasis by performing MRI or CT scan.

The contrasting oncological outcomes and responses to different conservative therapies of early-stage EC suggest that other factors should address fertility-preserving strategies in addition to histological staging. Not only the radiological and histological findings should be considered, but also cancer molecular panel and serum biomarkers, which could reflect the prognosis and the chance of response to therapies (Agusti *et al*. 2024).

The innovative FIGO staging (2023) was the first to encourage, even in biopsy specimens, the molecular pattern of all ECs following the ProMisE system, which identifies four classes of tumours, according to The Cancer Genome Atlas (Talhouk *et al*. 2017):

- POLE-mutated (ultra-mutated) with a better prognosis.
- MMRd, mismatch repair deficiency (hypermutated), with intermediate prognosis.
- Copy number low (non-specific mutation, NSPM), with intermediate/good prognosis.
- P53-mutated (copy number high), with poor prognosis.

Each subtype contributes to the risk stratification of EC and can guide the clinician in choosing adjuvant therapy after definitive surgery. Moreover, since 2023, the molecular characterisation influenced the tumoral FIGO staging: in early EC (stages I and II, based on preoperatory examinations), if a POLE mutation is found, the tumour is down-staged to IAm, regardless of the lympho-vascular invasion and the histological type (Berek *et al*. 2023). The concept of molecular-based prognostic stratification could be translated to fertility-sparing management, improving the accuracy of eligibility criteria and proposing therapeutic strategies tailored to the patient and her disease. The latest ESGO/ESHRE/ESGE guidelines suggest the ProMisE classifier for early-stage G1 tumours in young patients. However, limited scientific evidence and weak clinical feasibility affect its prognostic potential in low-risk diseases. Only immunohistochemical searching for MMRd tumours is mandatory to identify women at risk of Lynch syndrome, who have a higher rate of persistence/recurrence (Rodolakis *et al*. 2023).

An interesting review by Agusti *et al*. (2024) provides an overview of the prognostic value of the four molecular categories when opting for FST:

- POLE-mutated tumours show favourable outcomes, regardless of treatment approach.
- MMRd tumours seem to have a weaker response to progestin treatment. After initial regression, MMRd finding can be considered a red flag of high risk of recurrence.
- P53-mutated tumours appear to have the most unfavourable prognosis, with a rapid risk of progression. ESGO 2023 guidelines underline that the finding of p53 mutation could contraindicate FST.
- P53-wild type/NSMP tumours have a better prognosis in terms of CR and relapse rate than MMRd and p53-mutated cancers.

Their use in clinical practice still needs to be improved since only a few retrospective cohorts (less than 50 cases) with different oncological outcomes, therapeutic strategies, and follow-up duration are available (Agusti *et al*. 2024). However, these data provide interesting research insights for future clinical applications.

Moreover, even within the four categories of the ProMisE classifier, further immunohistochemical stratification should be performed, especially in more heterogeneous groups such as the NSPM. Oestrogen (ER) and progestin receptors (PR) are the most studied additional markers: their positivity seems to predict a higher response rate to hormone therapy, but the results are controversial, and their impact depends on the molecular group of the tumour (Agusti *et al*. 2024). Through immunohistochemistry, Li *et al*. (2023) demonstrated that patients undergoing FST and experimenting with recurrence after CR had significantly lower ER expression and a higher positivity to Ki67 than the group without recurrence. Interestingly, a cut-off value of 3.55 for the integrated index (ER/Ki-67) was a better predictor of EC recurrence after FST than a single immunohistochemical marker. A systematic review by Tanos *et al*. (2022) summarised all the immunohistochemical biomarkers proposed over the last decade to predict response to FST. PTEN and POLE mutations were prognostic factors of early-stage EC, showing favourable outcomes in women undergoing FST. MSI, CTNNB1, and K-RAS alterations represent fair prognostic factors of early-stage EC, still allowing FST, but with the knowledge that there is a higher relapse rate. PIK3CA, HER2, ARID1A, P53, L1-CAM, and FGFR2 are the poorest prognostic markers of early-stage EC, and in these cases FST may be contraindicated.

Even biomarkers from routine preoperative tests, such as hematological values, can predict aggressive tumour behaviour. The EC oncogenic pathway creates a chronic systemic inflammatory state, which can affect blood biochemistry values. In this regard, a recent retrospective multi-centre cohort study was performed by Vrede et al. (2024). The study design involved the monitoring of three blood values: anaemia (considered if haemoglobin level was <12.0 g/dl), thrombocytosis (>400,000/MMC platelets), and leukocytosis (leukocyte count > 10×109) in a group of patients with EC before surgery. The finding was that anaemia and thrombocytosis were significantly associated with high-risk tumour phenotypes according to the ESGO classification (Concin *et al.* 2021). Moreover, anaemia represented an independent risk factor for reduced disease-free survival (HR 2.31, 95% CI 1.19–4.50). Further studies could explore the interaction between molecular class type and haematological values in young women eligible for FST.

In conclusion, evaluating immunohistochemical, molecular, and hematological markers could be a topic of clinical interest in the diagnostic and therapeutic work-up of women with EC undergoing FST. Further research should focus on the ProMisE classifier and other molecular biomarkers to better stratify the risk classes in patients undergoing FST and align them with those undergoing definitive treatment. Given the low cost and wide availability of routine hematological preoperative testing, it is worth encouraging further work on the prognostic relationship between blood values and response to pregnancy-preserving therapies.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The authors reported there is no funding associated with the work featured in this article.

References

Agusti, N., Kanbergs, A. and Nitecki, R., 2024. Potential of molecular classification to guide fertility-sparing management among young patients with endometrial cancer. *Gynecologic oncology*, *24* (185), 1–4.

Berek, J.S., *et al.*, 2023. Endometrial cancer staging subcommittee, FIGO Women's Cancer Committee. FIGO staging of endometrial cancer: 2023. *International Journal of Gynecology & Obstetrics*, *162* (2), 383–394. PMID: 37337978.

Concin, N., *et al.*, 2021. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer*, *31* (1), 12–39. Epub 2020 Dec 18. PMID: 33397713.

Gullo, G., *et al.*, 2023. Fertility-sparing strategies for early-stage endometrial cancer: stepping towards precision medicine based on the molecular fingerprint. *International Journal of Molecular Sciences.*, *24* (1), 811. PMID: 36614253; PMCID: PMC9821405. https://ec.europa.eu/eurostat/web/products-eurostat-news/-/ddn-20210224-1

Li, L., *et al.*, 2023. Analysis of immunohistochemical characteristics and recurrence after complete remission with fertility preservation treatment in patients with endometrial carcinoma and endometrial atypical hyperplasia. *Archives of Gynecology and Obstetrics*, *307* (6), 2025–2031. Epub 2022 Jan 30. PMID: 35098335.

Ogunbiyi, M.O., *et al.*, 2024. The oncological and reproductive outcomes of fertility-preserving treatments for stage 1 grade 1 endometrial carcinoma: a systematic review and meta-analysis. *J Obstet Gynaecol*, *44* (1), 2294329. Epub 2023 Dec 21. PMID: 38126736.

Rodolakis, A., *et al.*, 2023. ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma. *Human reproduction open*, *2023* (1), hoac057. Feb 6 PMID: 36756380; PMCID: PMC9900425.

Siegel, R.L., *et al.*, 2020. Cancer statistics. *CA: A Cancer Journal for Clinicians*, *70*, 7–30. doi: 10.3322/caac.21590.

Talhouk, A., *et al.*, 2017. Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer. *Cancer*, *123* (5), 802–813. Epub 2017 Jan 6. PMID: 28061006.

Tanos, P., *et al.*, 2022. Biomolecular and genetic prognostic factors that can facilitate fertility-sparing treatment (FST) decision making in early stage endometrial cancer (ES-EC): a systematic review. *International Journal of Molecular Sciences.*, *23*, 2653.

Vrede, S.W., *et al.*, 2024. Abnormal preoperative haematological parameters in endometrial cancer; reflecting tumour aggressiveness or reduced response to radiotherapy? *Journal of Obstetrics and Gynaecology Research*, *44* (1), 2294332. Epub 2024 Jan 7. PMID: 38186008.

Yang, L., *et al.*, 2023. Time trend of global uterine cancer burden: an age-period-cohort analysis from 1990 to 2019 and predictions in a 25-year period. *BMC Womens Health*, *23* (1), 384. PMID: 37480027; PMCID: PMC10362563.

Luca Giannella, Camilla Grelloni and Andrea Ciavattini
Department of Woman's Health Sciences, Gynecologic Section, Polytechnic University of Marche, Ancona, Italy
lucazeta1976@libero.it