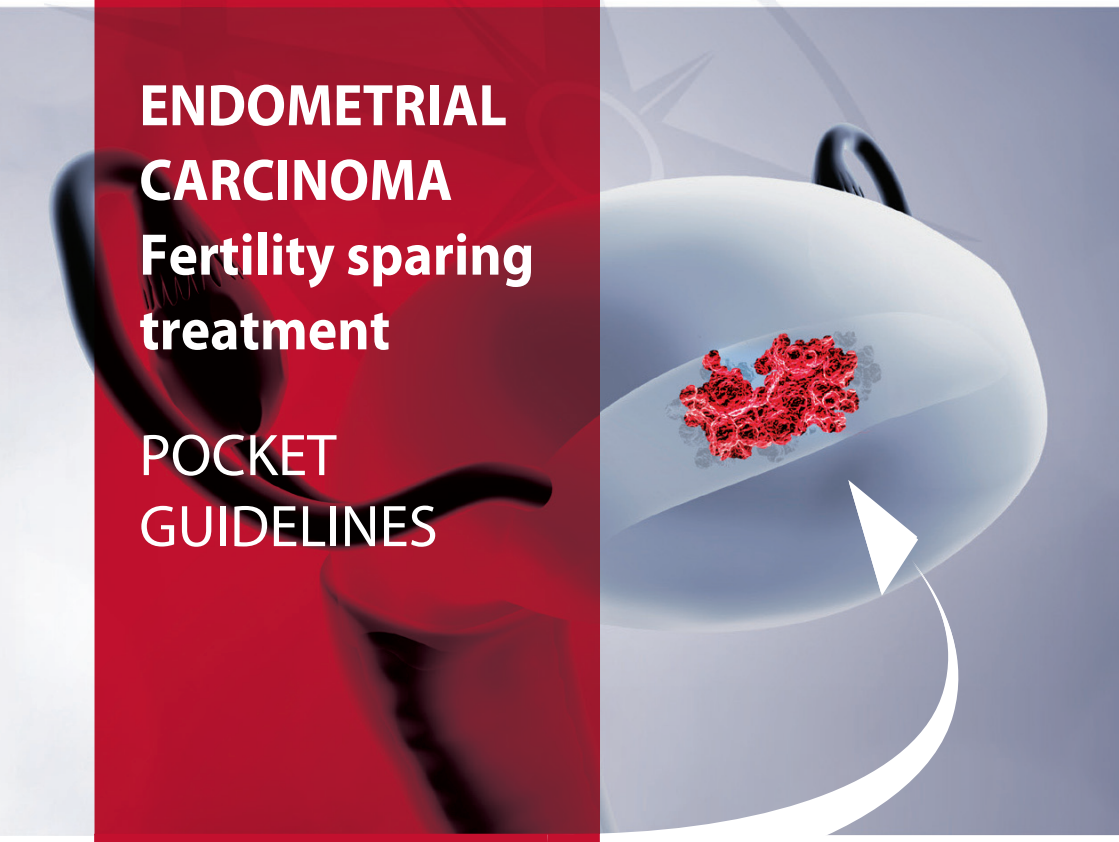
ESGO Guidelines
and Quality Indicators

ENDOMETRIAL CARCINOMA
Fertility sparing treatment

POCKET GUIDELINES



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ESGO
European Society of Gynaecological Oncology

POCKET GUIDELINES

Based on

ESGO/ESHRE/ESGE Guidelines for the fertility sparing treatment of patients with endometrial carcinoma

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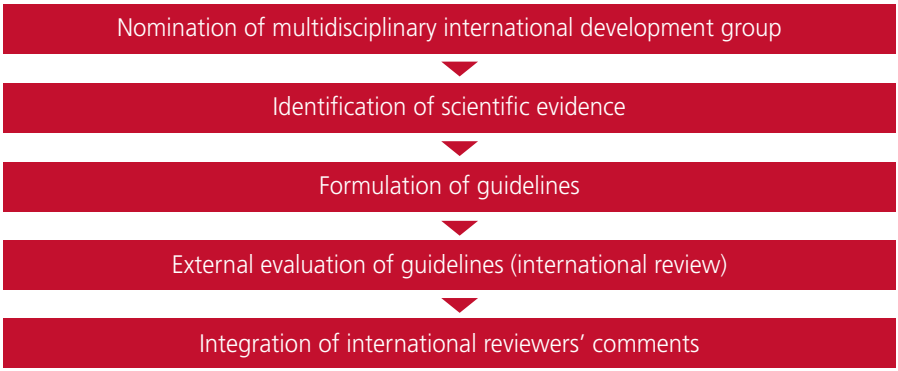
A collaboration was set up between the European Society of Gynaecological Oncology (ESGO), the European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE), aiming to develop clinically relevant and evidence-based guidelines focusing on key aspects of fertility sparing treatment (patient selection, tumour clinicopathological characteristics, medical treatment and special issues).

The guidelines were developed using a five-step process as defined by the ESGO Guideline Committee:



The objective of these ESGO/ESHRE/ESGE Guidelines is to improve the quality of care for women with endometrial carcinoma across Europe and worldwide. They are intended for use by all health professionals who are involved in the fertility sparing treatment of patients with endometrial carcinoma, across all allied disciplines.

These guidelines do not include any economic analysis of the strategies. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

To ensure that the statements were evidence-based, the current literature was reviewed and critically appraised. A systematic literature review of relevant studies published between September 2016 and September 2021 was carried out.

The guidelines were adopted if they were supported by sufficient high level of scientific evidence and/or when a large consensus among experts was obtained. An adapted version of the "Infectious Diseases Society of America-United States Public Health Service Grading System" was used to define the level of evidence and grade of recommendation for each of the recommendations:

LEVELS OF EVIDENCE

I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted, randomised trials without heterogeneity

II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity)

III Prospective cohort studies

IV Retrospective cohort studies or case-control studies

V Studies without a control group, case reports, and/or expert opinions

GRADES OF RECOMMENDATIONS

A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…), optional

D Moderate evidence against efficacy or for adverse outcome, generally not recommended

E Strong evidence against efficacy or for adverse outcome, never recommended

ESGO would like to thank the international development group for their constant availability, work, and for making possible the development of these guidelines for the fertility sparing treatment of patients with endometrial carcinoma (see below). ESGO is also very grateful to the 95 international external reviewers for their participation (list available on the ESGO website).

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TABLE OF CONTENTS

Patient selection

General recommendations

A — Patients with a pregnancy wish should be referred to specialized care, especially those with genetic syndrome.

A — Joint care and counselling with a multidisciplinary team of at least gynaecologic oncologists, fertility specialists, pathologists and radiologists should be proposed to all patients with a pregnancy wish.

Reproductive potential

B — No recommendations can be given based on the literature. However, the reproductive potential evaluation and consultation with fertility specialists should be performed prior to fertility sparing treatment.

Age - Specific age limits

A — Women should be counselled about their reduced chances of achieving a live birth with own gametes with increased age.

Health status, obesity

A — Following fertility sparing therapy for endometrial carcinoma, weight loss in overweight and obese women or maintaining a healthy body mass index (BMI) represent an important issue for improving the chances of pregnancy (natural or after assisted reproductive technologies) and live birth. Therefore, weight loss in overweight and obese women or maintaining a healthy BMI after fertility sparing treatment is strongly suggested as soon as possible.

Lynch syndrome

A — The presence of any concurrent/metachronous cancer should be determined.

A — Patients should be informed on the higher risk of persistence/recurrence as compared to other patients.

A — Fertility sparing treatment in women with Lynch syndrome should be discussed on a case-by-case basis.

Tumour clinicopathological characteristics

Review of initial pathology by an experienced histopathologist

A — A request for second opinion by experienced histopathologist is recommended if fertility sparing treatment is considered.

A — The G1, G2, G3 grading system is recommended. The binary grading system for endometrial carcinoma should not be used for these patients.

D — The use of immunohistochemistry (PTEN, ARID1A, etc.) for the evaluation of several biomarkers is not recommended for diagnostic purposes.

Differentiation of the tumour

A — Fertility sparing treatment of endometrioid endometrial carcinoma is considered for endometrioid endometrial carcinoma patients with grade 1, stage IA without myometrial invasion and without risk factors.

C — There is limited evidence for grade 2 endometrioid endometrial carcinoma. Therefore fertility sparing treatment should be discussed on a case-by-case basis.

Establishing a reliable histopathology

A — Hysteroscopic guided endometrial biopsy is preferred over blind biopsy for confirming diagnosis of endometrial carcinoma.

Myometrial invasion

A — Preoperative assessment of myometrial invasion in patients with endometrial carcinoma should be performed using magnetic resonance imaging (MRI) or transvaginal ultrasound (TVUS) by a specialized radiologist/sonographer. Standardized high-quality protocols for MRI should be used to reach the highest possible accuracy.

A — Computed tomography (CT) should not be used for preoperative assessment of myometrial invasion in patients with endometrial carcinoma.

Exclude extrauterine disease/synchronous or metastatic

B — MRI or CT scan are recommended for detecting pelvic or para-aortic lymph nodes and distant metastases.

B — Adnexal involvement should be ruled out by pelvic MRI or TVUS.

Treatment

Selection of medication

B — A combined approach consisting of hysteroscopic tumour resection, followed by oral progestins and/or levonorgestrel-intrauterine device (LNG-IUD), is the most effective fertility sparing treatment both in terms of complete response rate and live birth rate compared to other treatment options.

B — Gonadotropin-releasing hormone analogues should not be considered as a first line treatment.

The role of hysteroscopic resection

C — If an early and focal myometrial invasion (1-2 mm) is suspected from the resection material, a fertility sparing approach may be discussed on a case-by-case basis. In this circumstance, complete hysteroscopic lesion resection, followed by oral progestins and/or LNG-IUD, can be proposed as fertility sparing treatment.

Dose of progestins

B — Orally administered megestrol acetate at a dose of 160-320 mg/day or medroxyprogesterone acetate at a dose of 400-600 mg/day is recommended.

B — LNG-IUD at a dose of 52 mg, alone or in combination with oral progestins, is a safe and effective approach.

Duration of treatment

B — 6-12 months is the recommended duration of therapy within which a complete response should be achieved.

C — The maximum time to achieve complete response should not exceed 15 months.

B — In absence of any kind of response at 6 months, a multidisciplinary counseling is recommended for adapting the management on a case-by-case basis.

Response (partial vs. complete vs. no response)

B — Hysteroscopic resection followed by progestins either by oral and/or intra-uterine device administration is recommended to achieve both the highest complete response rate and the highest live birth rate.

A — Weight control during fertility sparing treatment is highly recommended to increase the chance of response.

Follow-up with maintenance treatment for patients willing or not willing to conceive immediately

C — Two consecutive endometrial biopsies showing complete response with a minimal interval of 3 months are necessary to consider the success of the fertility sparing treatment.

A — The complete response is mandatory to consider follow-up with maintenance treatment until pregnancy plan.

B — Clinical pelvic examination and ultrasound scan are recommended at every 3-month follow-up visit.

B — Endometrial histological assessment should be performed every 3-6 months by hysteroscopy according to the results of imaging.

C — MRI could be considered on a case-by-case basis.

Pregnancy

B — Women undergoing fertility sparing treatment for atypical endometrial hyperplasia or endometrial carcinoma should be encouraged to actively pursue to conceive as soon as the complete response is achieved.

B — Assisted reproductive technology should be considered to improve success rate and reduce the interval to conception without a higher risk of recurrence.

C — However, natural conception may be considered in women with good reproductive potential within a defined time (6-9 months).

B — Close surveillance by a multidisciplinary team should be continued and maintenance therapy with LNG-IUD should be recommended to women who decline surgery after delivery and who do not plan their second pregnancy immediately after the first one.

Recurrence rate after fertility sparing treatment

B — Progestins or LNG-IUD may be equal in terms of risk of recurrence after fertility sparing treatment for endometrial carcinoma.

Definitive and completion surgeries

A — Definitive surgery is recommended in case of non-responders, inability to conceive, recurrence or disease progression.

B — For patients with a strong desire to preserve fertility, a second conservative approach can be considered on a case-by-case basis.

A — Completion surgery is recommended after completing childbearing.

B — Removal of ovaries should be considered on a case-by-case basis.

Special issues

Estrogen and/or progesterone receptors status

C — Estrogen receptors (ER) and progesterone receptors (PR) expressions seem to be predictive of response in conservative treatment and could be useful for patient counselling.

C — Negative ER and PR expressions are not a contraindication for fertility sparing treatment.

Molecular profiling of early onset endometrial carcinoma and correlation with response to treatment

B — Performing the ProMisE molecular classifier in all young patients with grade 1, low-stage endometrial carcinoma who wish to preserve fertility is encouraged, although available data do not allow clinical applicability.

A — Immunohistochemistry for the identification of mismatch repair-deficient tumours is mandatory in order to identify patients at high risk for Lynch syndrome.

A — If a Lynch syndrome is identified, patients should have an appropriate counselling on the risk of developing additional cancers.

A — In a tumour with p53abn phenotype, testing for MSH-H and *POLE* mutation should be considered in order to define whether the tumour belongs to the multiple classifiers or to the copy number high molecular subgroup.

D — In women harbouring copy number high (p53abn) tumours, conservative therapy would be inappropriate.

NOTES

Access full ESGO Guidelines: www.esgo.org/explore/guidelines

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