Fertility-sparing treatment and follow-up in patients with cervical cancer, ovarian cancer, and borderline ovarian tumours: guidelines from ESGO, ESHRE, and ESGE

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The European Society of Gynaecological Oncology, the European Society of Human Reproduction and Embryology, and the European Society for Gynaecological Endoscopy jointly developed clinically relevant and evidence-based guidelines focusing on key aspects of fertility-sparing strategies and follow-up of patients with cervical cancers, ovarian cancers, and borderline ovarian tumours. The developmental process of these guidelines is based on a systematic literature review and critical appraisal involving an international multidisciplinary development group consisting of 25 experts from relevant disciplines (ie, gynaecological oncology, oncofertility, reproductive surgery, endoscopy, imaging, conservative surgery, medical oncology, and histopathology). Before publication, the guidelines were reviewed by 121 independent international practitioners in cancer care delivery and patient representatives. The guidelines comprehensively cover oncological aspects of fertility-sparing strategies during the initial management, optimisation of fertility results and infertility management, and the patient's desire for future pregnancy and beyond.

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Introduction

Fertility preservation has emerged over the past three decades as a major issue in the management of adult and paediatric cancers. During the past 5 years, several guidelines, issued by renowned societies (such as the European Society of Medical Oncology, the European Society of Human Reproduction and Embryology, the PanCareLIFE Consortium, and the International Late Effects of Childhood Cancer Guideline Harmonization Group) have been published on the topics of fertility preservation and cancer management,[1–3] and have mainly focused on general health-care organisation to improve fertility in adult, child, adolescent, or young adult patients, and on gametes (ie, oocytes, ovary, and sperm) preservation and gonadotoxicity of radiotherapy or drugs. Gonadotoxicity induced by systemic or radiotherapies will not be included in this Policy Review. Recent evidence-based guidelines from the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) provide comprehensive information on all relevant issues of diagnosis and treatment in cervical cancer in a multidisciplinary setting. Although these guidelines address fertility-sparing treatment, there was relevant consideration to further extend the published guidance on this topic.[4] 6 years ago, a strong collaboration was established between the 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 treatments of patients with gynaecological malignancies. A first article focusing on endometrial carcinoma was published in 2023.[5] In this Policy Review, we address three main topics. First, we aim to analyse the indications of fertility-sparing treatment including conservative surgeries, stage-by-stage and histotype-by-histotype (if required). As endometrial cancers have recently been covered by earlier publications, they are not included in this Policy Review. We then focus on ovarian tumours (ie, borderline, non-epithelial, and epithelial cancers) and cervical cancers in which modalities and indications of conservative treatments are highly debated. The second major topic we address is the optimisation of fertility results and management of infertility if occurred (eg, can assisted reproductive technologies [ART] be used in such patients previously treated for cancers?). Finally, we assess aftercare management, which presents major practical questions (eg, when to give authorisation to start trying to conceive? Is a completion surgery needed? How to follow-up with patients?). The latter two topics have not previously been covered concretely in guidelines because strong evidence is scarce and the daily practice of experts managing patients is based on experience, conviction, or habit.

Guidelines, including those covering the practical and pragmatic aspects of fertility-sparing and cancer management (ie, the questions asked by patients on a daily basis), are urgently required. The guidelines are intended to improve the quality of fertility-sparing strategies in ovarian and cervical cancers and harmonise them to be used by all health professionals involved in the fertility-sparing treatment of patients with cervical cancers, ovarian cancers, or borderline ovarian tumours, across all allied disciplines.

Definition of the surgical perimeter and topics covered

Fertility-sparing surgery, in the ESGE, ESHRE, and ESGO guidelines, is based on the preservation

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of the uterus and at least one part of one ovary, with the aim to achieve (spontaneous) pregnancy. When both ovaries are macroscopically involved (or at greater oncological risk of bilateral spread) in ovarian tumours, isolated uterine preservation (with bilateral salpingo-oophorectomy) is discussed. These guidelines exclude the procedures used to protect gonads and maintain endocrine functions of the ovaries (ovarian transposition, gonadotrophin hormone-releasing hormone agonists, etc), combined with ovarian transposition, uterine transplantation, and surrogate pregnancy. The guidelines also do not include any economic analysis of the strategies discussed in this Policy Review. Tumour histological subtypes and staging are defined according to the WHO Classification of Tumours[6] and the International Federation of Gynecology and Obstetrics (FIGO) staging systems (2021[7] for the ovary, tube, and peritoneum, and 2019[8] for the cervix).

Recommendation development process

The evidence-based guidelines were developed using a robust development process, including a multidisciplinary international development approach, a systematic literature search, and an external review process performed by a large panel of physicians and patients (figure 1). ESGO, ESHRE, and ESGE nominated this multidisciplinary panel of physicians based on those who have shown leadership through their expertise in clinical care, research, and their dedication to the topics addressed in this Policy Review (appendix p 3). The international group of experts in charge of developing the guidelines was chaired by representatives of ESGO (PM), ESGE (GS), and ESHRE (MG).

A systematic, unbiased literature review, which represents a cornerstone for developing evidence-based guidelines, was carried out by an experienced methodologist using MEDLINE (appendix p 4). Literature published between Jan 1, 2003, and June 1, 2023, was reviewed and critically appraised. Priority was given to high-quality systematic reviews, meta-analyses, and randomised controlled trials, but studies with less evidence were also evaluated. Editorials, letters, in vitro studies, and publications in languages other than English were excluded. The reference list of each identified article was also reviewed for other potentially relevant papers.

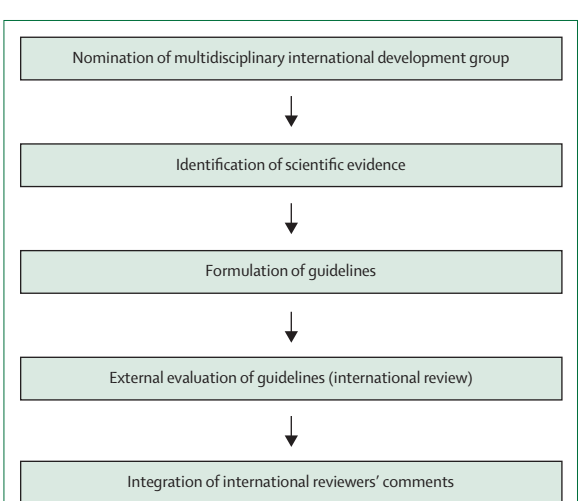

Figure 1: **Development process of evidence-based guidelines**

Three subgroups, including experts of the development group, were created according to the topics addressed in this Policy Review. Based on the collected evidence and clinical expertise, the subgroups drafted guidelines for their assigned topics. The guidelines were discussed by the whole group and retained if they were supported by sufficiently high-level scientific evidence and when a large consensus (75% agreement) among experts was obtained. An adapted version of the Infectious Diseases Society of America-US Public Health Service Grading System[9,10] was used to define the level of evidence and grade of recommendation for each of the recommendations (table).

The external evaluation of the guidelines (international review) was another key step of the development process. ESGO, ESHRE, and ESGE established a large multidisciplinary panel of practising clinicians selected according to their expertise, as well as their involvement in clinical practice and research to act as independent expert reviewers for the guidelines. To ensure a global perspective, physicians from Asia, Europe, north Africa, North America, the Middle East, and South America were involved. Two patients with cervical cancer or ovarian tumours were also included. The independent reviewers were asked to evaluate each recommendation according to its relevance and feasibility in clinical practice. Patients were approached separately and asked to evaluate each recommendation according to their experience, preferences, and feelings. Reviewers were asked to provide comments or suggestions if they did not agree with the proposed guidelines. In total, evaluations from 121 external reviewers were collected and discussed by the development group members to finalise the guidelines' development process (appendix p 5).

Findings

The guidelines detailed in this Policy Review comprehensively cover oncological aspects of fertility-sparing strategies during the initial management of cancer, optimisation of fertility results, infertility management, and the patient's desire for future pregnancy and beyond. A summary of the guidelines and of evidence supporting the guidelines are included in the appendix (pp 7–37).

General recommendations

Counselling with a reproductive specialist who has an in-depth understanding of the patient and couple's history is recommended before considering

fertility-sparing treatment and pregnancy seeking (level of evidence V, grade of recommendation A; table). The aim of fertility-sparing surgery is to enable patients to have unassisted or assisted pregnancies with their uterus and their own or donated oocytes (V, A). Fertility-sparing surgery and treatment planning should be performed exclusively by teams with a strong collaboration between gynaecological oncologists and reproductive medicine specialists (V, A). Pathological expert review is recommended in all patients if the diagnosis and associated treatment could impair fertility (V, A). Detailed description of the initial surgery should be provided (endobag, upper abdomen description, etc; V, A). The main steps for the selection of patients for considering fertility-sparing treatment are described in figure 2.

Oncological aspects of fertility-sparing strategies during the initial management of cervical cancer

Oncological selection criteria

The mandatory imaging tests to assess oncological criteria are pelvic MRI (preferred; evaluated by a dedicated gynaecological radiologist) or expert sonography. The following information is required: tumour size, depth of stromal invasion, distance between cranial edge of tumour and internal cervical orifice, and any extra cervical extension or suspicious nodes (III, A). Radiological assessment by CT or PET-CT could be performed to exclude any distant metastatic disease (II, B). Cervical conisation is the method of choice for staging in early cervical cancer and could be associated with lymph node staging according to the ESGO–ESTRO–ESP guidelines (II, B). Conisation should be performed if no gross lesion is noted (III, B).

Surgical and pathological criteria

Radical trachelectomy with removal of a part of parametria is not recommended for stage IB1 disease fulfilling all the strict inclusion criteria of the ConCerv trial[11] (ie, stage IA2-IB1 as defined by the 2009 FIGO staging system, squamous cell at any grade or adenocarcinoma at grade 1 or 2, tumour size ≤2 cm, no lymphovascular space invasion [LVSI], negative imaging for metastatic disease, depth of invasion ≤10 mm, and conisation margins and endocervical curettage negative for malignancy or high-grade dysplasia; III, E). Radical trachelectomy is recommended for stage IB2 disease by use of an abdominal approach (eg, laparotomy or mini-invasive approaches [robotic-assisted or pure laparoscopic approaches]; IV, B). Lymph node staging strategies for stage IB1 and IB2 diseases should follow the ESGO–ESTRO–ESP guidelines (IV, B). Negative margins (a non-fragmented specimen, with at least 1 mm histological-free margin from carcinoma or dysplasia) are mandatory (III, A). A non-fragmented cone is crucial for pathological evaluation. The base of the cone should encompass the visible gross lesion on the ectocervix with at least 1 mm histological margin. The height of the cone (centre of cone base to vertex) should be at least 10 mm. Cones can be oriented with a suture at the midpoint of the anterior cervical lip (also

	Evidence and recommendations
Levels	
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 or large randomised trials with a suspicion of bias (lower methodological quality than level I), 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 control groups, case reports, or experts' opinions
Grades	
A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy, but with minimal clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Table: **Levels of evidence and grades of recommendations**

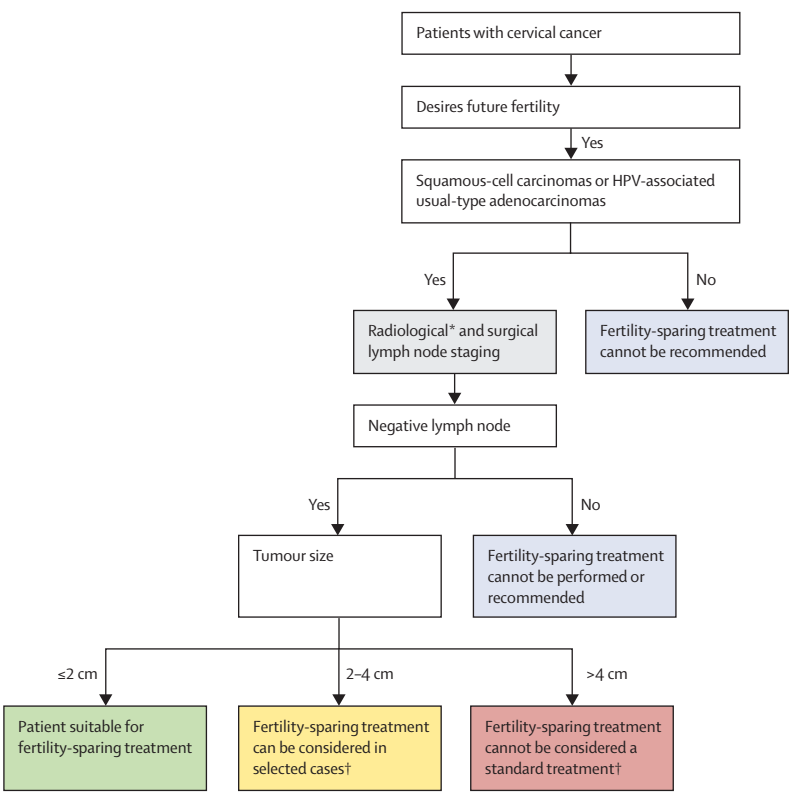

Figure 2: **Selection of patients with cervical cancer for fertility-sparing treatment**
HPV=human papillomavirus. *Pelvic MRI (preferred; evaluated by a dedicated gynaecological radiologist) and expert sonography are mandatory imaging tests. Radiological assessment by CT or PET-CT could be performed to exclude any distant metastatic disease. †Pelvic lymph node staging (sentinel lymph node) should always be the first step in each fertility-sparing therapy procedure (except for T1a1 lymphovascular space invasion negative disease). All sentinel lymph nodes from both sides of the pelvis and any suspicious lymph nodes should be sent for frozen section. If sentinel lymph node cannot be detected on either pelvic side, a systematic pelvic lymphadenectomy should be performed on that side. Intraoperative assessment of lymph node status is highly recommended.

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See Online for appendix

called the 12 o'clock suture; IV, B). A negative endocervical biopsy or curettage above the conisation or trachelectomy is required (IV, B). Pathologists are encouraged to assign a Silva pattern classification for human papillomavirus (HPV)-associated usual-type adenocarcinoma tumours (pattern A is the most favourable; pattern B without LVSI is also favourable; IV, C). Negative pelvic nodal status is mandatory for any fertility-sparing therapy. For assessing the pelvic nodal staging, ESGO–ESTRO–ESP guidelines should be followed (IV, A). Pelvic nodal staging is not indicated in T1a1 LVSI-negative tumours that have negative margins on conisation (IV, D). Intraoperative frozen section of cone margins can be considered to tailor the surgery (IV, B).

Favourable oncological selection criteria

The following seven criteria should be met before considering fertility-sparing management. First, assignment of patients to favourable selection criteria is based on all clinicopathological variables (IV, B). Second, confirmed histology on cervical biopsy or conisation is consistent with squamous cell carcinoma (all grades) or usual-type HPV-associated adenocarcinoma (all grades) with no more than 10 mm stromal invasion (IV, B). Third, absence of LVSI is a favourable pathological biomarker (III, B). Fourth, no evidence of any metastasis is required (IV, A). Fifth, largest measurement of a tumour is 2 cm by imaging or clinical exam (IV, B). Sixth, free margins on final pathology are mandatory (III, A). Finally, no evidence of tumour involvement of the internal cervical orifice and cranial extent of cervical tumour is 1 cm or more from the internal cervical orifice on imaging (IV, B).

Unfavourable oncological selection criteria

At least one of the following criteria should be met: any histological type other than squamous cell carcinoma and usual-type HPV-associated adenocarcinoma (mucinous-type HPV-associated carcinomas, gastric-type cervical adenocarcinoma, mesonephric carcinoma, small-cell neuroendocrine carcinoma, and clear cell carcinoma; IV, C); confirmed pelvic nodal involvement, extracervical tumour extension, evidence of tumour beyond the cervical ring, or metastasis (IV, B); the largest tumour measurement is more than 4 cm by imaging or clinical exam (IV, B); FIGO stage is IB3 or more (IV, B); tumour cranial extent is less than 5 mm from, or involves, the internal cervical orifice or lower uterine segment by imaging (IV, B); intraoperative frozen-section assessment of the resected cervical specimen for assessing the upper resection margin reveals a positive margin from the internal cervical orifice with inability to achieve a wider margin (IV, B); or histologically confirmed endocervical margin, endocervical curettage above resection, or endometrial involvement on final pathology (IV, B).

Oncological selection criteria acceptable in selected cases

At least one of the following criteria should be met: tumour size is 2–4 cm by exam or imaging (IV, C); stromal invasion by conisation is more than 10 mm but has negative margins (IV, C); evidence of deep cervical stromal invasion on MRI or sonography (IV, B); tumour cranial extent is 5–10 mm from internal cervical orifice by imaging (IV, C); trachelectomy specimen margin reveals a 5–10 mm tumour-free margin from the internal cervical orifice (IV, B); Silva pattern C of HPV-associated usual-type adenocarcinoma (data are scarce on pattern B with LVSI; IV, C).

Neoadjuvant chemotherapy for patients with stage IB2 cerival cancer

Neoadjuvant chemotherapy has been used by various investigators as an alternative to radical trachelectomy for selected patients with stage IB2 (2–4 cm) cervical cancer (IV, C). Various chemotherapy regimens have been used to reduce cervical tumour burden and allow for a satisfactory resection of the primary tumour with conisation and simple or radical trachelectomy (IV, C). Retrospective data suggest that abdominal radical trachelectomy has the lowest recurrence rate for patients with stage IB2 cervical cancer (IV, C). Ongoing prospective trials with platinum and paclitaxel will clarify the validity of neoadjuvant chemotherapy in fertility-sparing treatment of stage IB2 disease (IV, C). Including patients with stage IB2 cervical cancer in ongoing trials is encouraged to evaluate the safety of neoadjuvant chemotherapy (V, B). Confirming pathological-negative bilateral pelvic nodes (sentinel lymph node or lymphadenectomy) before starting neoadjuvant chemotherapy allows for the most accurate staging and selection of appropriate candidates for neoadjuvant chemotherapy approach (IV, B). Preoperative imaging with pelvic MRI and whole body PET-CT is favoured (IV, B).

Oncological aspects of fertility-sparing strategies during the initial management of ovarian cancer

General recommendations

If bilateral oophorectomy is needed, uterine-sparing surgery can be considered assuming normal endometrial (preferably evaluated by hysteroscopy) and serosal evaluation (IV, B).

Favourable oncological selection criteria for ovarian preservation

One of the following criteria should be met (figure 3; IV, B): borderline ovarian tumour all stages (non-invasive peritoneal implants) regardless of ovarian microinvasion; germ cell tumours (all stages); granulosa cell tumours stage IA and IC1; Sertoli-Leydig cell well-and-moderately differentiated tumours stage IA; low-grade serous and low-grade endometrioid carcinomas stage IA and IC1; high-grade serous carcinoma stage IA; mucinous carcinoma expansile subtype stage IA and IC1; mucinous carcinoma infiltrative stage IA; or clear-cell carcinoma stage IA and IC1.

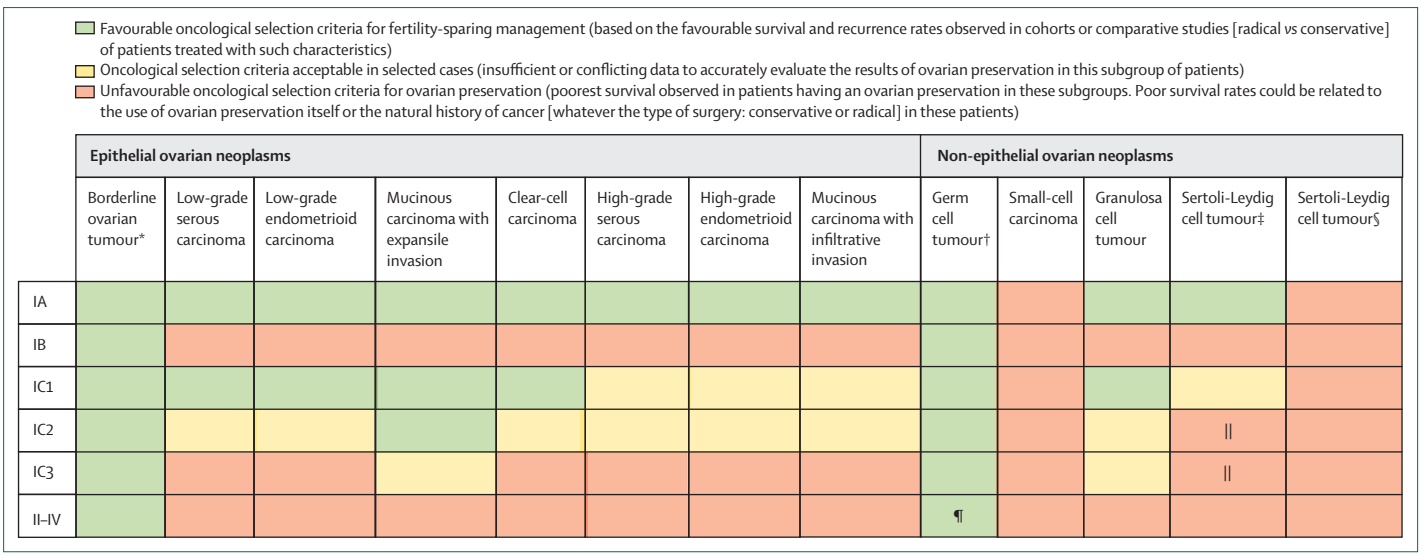

Figure 3: **Indications for in vivo ovarian tissue preservation in ovarian neoplasms according to histological type and stage of the disease**
*Non-invasive peritoneal implants. †Includes immature teratoma, dysgerminoma, and yolk-sac tumours. ‡Well-and-moderately differentiated. §Poorly differentiated. ¶For grades 2 and 3 immature teratoma stage II–IV, fertility-sparing data are scarce. ||For Sertoli-Leydig cell tumour stage IC2 and IC3, fertility-sparing data are scarce.

Unfavourable oncological selection criteria for ovarian preservation

One of the following criteria should be met (figure 3; IV, B): invasive epithelial ovarian tumours stage IB and II–IV; low-grade serous carcinoma stage IC3; low-grade endometrioid carcinoma stage IC3; high-grade serous and high-grade endometrioid carcinomas stage IC3; clear cell carcinoma stage IC3; mucinous carcinoma infiltrative stage IC3; small-cell carcinoma hypercalcaemic type; granulosa cell tumour stage IB and II–IV; Sertoli-Leydig cell tumours well-and-moderately differentiated at stages IB and IC2–IV, and poorly differentiated at all stages.

Oncological selection criteria acceptable in selected cases

One of the following criteria should be met (figure 3; IV, C): low-grade serous and low-grade endometrioid carcinomas stage IC2; mucinous carcinoma expansile subtype stage IC3; clear cell carcinoma stage IC2; high-grade serous and high-grade endometrioid carcinomas stage IC2; mucinous carcinoma infiltrative stage IC1 and IC2; granulosa cell tumour stage IC2 and IC3; Sertoli-Leydig cell tumours, well differentiated and moderately differentiated at stages IB and IC1; or tubo-ovarian carcinoma (unilateral) or serous tubal intraepithelial carcinoma in patients younger than 40 years with high-risk predisposition germline mutation.

Salpingo-oophorectomy versus cystectomy in selected cases of borderline ovarian tumours

Bilateral ovarian cystectomy with macroscopic healthy ovarian tissue sparing in bilateral serous and seromucinous borderline ovarian tumours can be considered (IV, B). Unilateral salpingo-oophorectomy and cystectomy with macroscopic healthy ovarian tissue sparing are both acceptable strategies for unilateral serous and seromucinous borderline ovarian tumour. In case of cystectomy, patients should be counselled about the risk of local and ovarian recurrence of up to 30% with no effect on overall survival, but better fertility results (IV, B).

Optimisation of fertility results and infertility management

Reproductive medicine specialist consultation

Individuals who wish to preserve their fertility should be offered reproductive counselling before the beginning of any oncological treatment (IV, B). The reproductive medicine specialist should be part of the treatment decision process and be consulted when treatment plans are changing or family planning starts. Creation of a specific multidisciplinary team is encouraged (V, A).

Reproductive medicine specialist consultation in patients with ovarian cancer and high-risk genetic predisposition

Patients who carry a high-risk genetic predisposition for ovarian cancer should have similar fertility preservation counselling compared with non-carriers (figure 3), including the information about transmission to the offspring (V, A). If fertility preservation is considered, ovarian stimulation followed by oocyte or embryo cryopreservation is the treatment of choice in patients who carry a high-risk genetic predisposition as it does not increase the individual risk of developing new hormone-dependent cancers (IV, B). There are no data on oncological safety of ovarian tissue reimplantation in patients who carry a high-risk genetic predisposition, but cryopreservation of ovarian tissue might be considered

(V, C). After completion of family planning or at the recommended time of pelvic prophylactic surgery, salpingo-oophorectomy, with or without hysterectomy, should be performed in patients who carry a high-risk genetic predisposition (IV, B). Patients who carry a high-risk genetic predisposition could be referred for preconception and preimplantation genetic-testing counselling (V, C).

Evaluating ovarian function in patients before cancer treatment

The assessment of ovarian reserve should be done with the same methods as in women without cancer (eg, serum anti-Müllerian hormone and antral follicle count), although the interpretation of results might be difficult in patients with ovarian tumours (V, B). The age of the patient is more important than anti-Müllerian hormone and antral follicle count in planning fertility-sparing treatment. Pretreatment ovarian reserve markers alone should not be used as treatment guide for fertility-sparing surgery (IV, D).

Fertility preservation methods in first-line treatment settings

Ovarian tumours

Ovarian stimulation followed by egg retrieval can be offered to patients with ovarian cancer with favourable prognostic factors considering histological diagnosis, hormone sensitivity, cancer stage, and oncological prognosis (figure 3; IV, C). Ovarian stimulation followed by egg retrieval for fertility preservation is not recommended before final histological confirmation of a possibly malignant or borderline ovarian mass (V, D). For primary ovarian neoplasms, it is recommended that ovarian stimulation and oocyte cryopreservation be performed after completing staging surgery and determining the histological diagnosis, hormone sensitivity, cancer stage, and oncological prognosis (figure 3; IV, B). Ovarian tissue freezing and immature oocytes retrieval for ex vivo in vitro maturation and further mature oocyte vitrification during surgery in case of bilateral oophorectomy could be offered (V, C). Ovarian stimulation followed by oocyte retrieval is not contraindicated in patients previously treated for stage I ovarian borderline tumours, even in cases of abnormal-appearing residual ovary that will be subjected to stimulation (V, D). Ovarian stimulation followed by oocyte retrieval (even in cases of abnormal-appearing residual ovary) is not contraindicated in patients with advanced stage borderline ovarian tumours, as long as there has been a complete resection and pathological evaluation (confirming non-invasive implants) of visible peritoneal lesions (V, D). The timing of ovarian stimulation and egg retrieval when adjuvant chemotherapy for ovarian cancer is planned depends on multidisciplinary discussion and can be performed ideally before chemotherapy or in rescue at least 6 months after chemotherapy (post-treatment fertility preservation; V, B). In cases of borderline ovarian tumour, biomarkers of the tumour (*BRAF*, oestrogen receptor, *KRAS*, etc) should not be used as a contraindication for considering ovarian stimulation (indication and protocol; V, D). In cases of low-grade serous or ovarian endometrioid adenocarcinoma or granulosa cell tumour, the ovarian stimulation protocol based on co-treatment with aromatase inhibitors should be a first choice (figure 3; IV, B).

Cervical cancers

For all patients with cervical cancer eligible for fertility-sparing management, ovarian stimulation followed by oocyte retrieval can be discussed for women without ovarian involvement treated by radiotherapy, brachytherapy, or hysterectomy in accordance with the legal country-specific regulations regarding surrogate pregnancy (V, C). Special attention is needed for ovarian stimulations and transvaginal oocyte retrieval in the presence of active cervical neoplasia. Transvaginal puncture and retrieval might be possible in selected cases with minimal tumour involvement. However, it should be avoided in cases with extensive upper vaginal disease to minimise the theoretical risk of iatrogenic cancer spread during the procedure. A transabdominal laparoscopic approach or open approach might be an option. Transabdominal approach for oocyte retrieval has been suggested as a safe and efficacious procedure (IV, C).

Fertility preservation methods in cases of recurrence

Fertility evaluation for patients with apparent recurrent, borderline ovarian tumours who wish to preserve their fertility is mandatory before any treatment in gynaecological oncology centres with comprehensive multidisciplinary expertise within a multidisciplinary team, including a reproductive medicine specialist (V, A). Ovarian stimulation followed by oocyte retrieval in cases of recurrent stage I borderline ovarian tumour with no evidence of peritoneal disease is feasible before potential definitive surgery (V, C). Ovarian stimulation followed by oocyte retrieval in cases of recurrent advanced stage borderline ovarian tumour is feasible as long as there has been a complete resection and pathological evaluation (confirming non-invasive implants) of visible peritoneal lesions and normal-appearing abdominopelvic imaging (CT or MRI scan) suggesting the absence of obvious implants before the eventual stimulation (V, C).

For malignant germ cell tumours, fertility preservation strategy should be discussed on an individual basis in a multidisciplinary team for women previously treated for an immature teratoma and presenting a recurrence highly suspicious of benign teratoma or growing teratoma syndrome (V, B). In cases of a suspected recurrence of sex cord tumours, fertility preservation strategies should not be considered (V, D).

Evaluating ovarian function

It is important to recognise the limitations of serum anti-Müllerian hormone concentrations and antral follicle count as predictors of pregnancy, either through natural conception or after ART (V, B). Regular measurement of serum anti-Müllerian hormone concentrations after cancer treatment can be used to indirectly estimate the degree and evolution of the ovarian follicular pool and ovarian response to stimulation (V, C).

What should be offered to patients after treatment?

Desire for immediate pregnancy

If fertility-sparing surgery did not affect the possibility of unassisted conception, patients are advised to attempt spontaneous conception for at least 6 months before being referred to a reproductive medicine specialist. Patients with a history of infertility or inability to conceive spontaneously should be referred to a reproductive medicine specialist as soon as possible (V, B).

No immediate pregnancy desired

Patients treated for ovarian tumours could be referred to a reproductive medicine specialist for counselling (V, C). In case of a previous history of infertility or inability of natural conception due to surgery, patients should be referred to a reproductive medicine specialist to discuss oocyte or embryo freezing (V, B). Patients who underwent fertility-sparing surgery for borderline ovarian tumours, including those with micropapillary or microinvasive features (who still have at least one ovary), should be advised about the availability of reproductive medicine specialists and referred as needed (figure 3; V, B). Patients who underwent fertility-sparing surgery for ovarian cancer (who still have at least one ovary) and are considered to have a favourable oncological prognosis should be advised about the availability of reproductive medicine specialists and referred if applicable, taking into account histological diagnosis, hormone sensitivity, stage, and oncological prognosis (figure 3; V, B).

Oocyte vitrification

When oocyte vitrification is considered after fertility-sparing surgery alone, ovarian reserve assessment should be performed at least 6 months after surgery to allow recovery (V, B). When oocyte vitrification is considered after chemotherapy, ovarian reserve assessment should be performed after at least 6 months (V, B).

Desire for a pregnancy and beyond

When should oncological authorisation be granted?

All patients with borderline ovarian, epithelial, or non-epithelial tumours should be advised according to the age of the patient, stage of disease, pathology, unilateral or bilateral localisation of the tumour, and mode of surgery (eg, cystectomy *vs* oophorectomy; IV, A). Patients with cervical cancer treated with any kind of surgery (eg, trachelectomy or conisation) are advised not to attempt pregnancy within the first 6 months after surgery (V, C). Spontaneous pregnancies can be encouraged in patients with a borderline ovarian tumour immediately after the fertility-sparing surgery (IV, B). Patients needing fertility treatment can be referred for ART in cases of a low-stage borderline ovarian tumour immediately after fertility-sparing surgery (IV, B). Patients needing fertility treatment can be referred for ART in cases of advanced-stage borderline ovarian tumour after complete resection and absence of invasiveness of implants immediately after fertility-sparing surgery (IV, B). Patients with a borderline ovarian tumour at high risk of relapse could be referred immediately after fertility-sparing surgery for oocyte or embryo cryopreservation (IV, C). Patients with epithelial ovarian cancer might be advised to become pregnant 1 year after the completion of treatment with negative follow-up (IV, C). Patients with non-epithelial, early-stage ovarian cancer might be advised to become pregnant after the first 6 months of a negative follow-up after the fertility-sparing procedure (IV, C). For patients with non-epithelial ovarian cancer needing fertility treatment, ART can be performed after the first 6 months of a negative follow-up after the fertility-sparing procedure (IV, C). Regardless of cancer type, patients should be advised that they are not limited to one pregnancy (V, A).

Cervical cancer

Frequencies of follow-up after fertility-sparing management

Follow-up is the same as for any patient with cervical cancer; namely, every 3–4 months for 2 years, every 6 months for another 3–5 years, and then annually (IV, B). Reduction of frequency of follow-up could be proposed in cases of negative HPV testing after conservative surgery (IV, C).

Follow-up procedures after fertility-sparing management

Physical examination should be performed, including bimanual pelvic examination every 3–4 months for the first 2 years, every 6 months thereafter until the fifth year, and then annually. Cytology plus HPV testing should be performed after 6 months, then annually (IV, B). Colposcopy should be performed in cases of abnormalities at cytology and a biopsy sample should be taken for positive results from HPV testing (IV, B). HPV vaccination should be encouraged (V, B). MRI (preferably evaluated by a dedicated gynaecological radiologist) is mandatory at 6 months and 12 months, and then when clinically indicated thereafter (IV, A). Transvaginal ultrasonography, with or without transrectal ultrasonography, is an option when performed by an experienced sonographer (IV, C). PET-CT can be considered in cases of suspicion of a recurrence (III, B). There is no evidence to recommend the routine use of squamous cell carcinoma antigen in follow-up (V, C).

Specific requirements for follow-up during pregnancy and maternal surveillance

A surgery requiring a large cervical excision should be accompanied by a permanent cerclage (IV, B). Progesterone supplementation in pregnancy after fertility-sparing surgery for cervical cancer is recommended to prevent preterm birth (IV, B). Patients with and without a permanent cerclage should be assessed for cervical incompetence during pregnancy by an experienced obstetrician (IV, B). Patients treated only with a large or repeat conisation should be evaluated for cervical incompetence or competence by an experienced obstetrician (IV, B). MRI can be performed when clinically relevant (IV, B). Follow-up visit consists of a physical examination and cytology plus HPV testing (co-testing) in early pregnancy unless it was performed within the last year (IV, B). Colposcopy should be performed when indicated from cytology or HPV testing and from clinical implications (IV, B). Transvaginal ultrasonography, with or without transrectal ultrasonography, should be performed by an experienced sonographer when clinically indicated (IV, B). Elective caesarean section should be considered for delivery in patients with history of invasive cervical cancer (IV, A). Breastfeeding is recommended, as in the general population, and should not be discouraged (IV, B).

Need for completion surgery after childbearing

Completion surgery after childbearing with no evidence of disease is not recommended (V, D). Hysterectomy should be offered only in cases where follow-up is not feasible (cervical stenosis and patient incompliance) and in cases of persistent, high-risk, HPV-positive test results (IV, B).

Indications and modalities for hormone replacement therapy after completion surgery or bilateral salpingo-oophorectomy plus uterine preservation

Patients with premature ovarian insufficiency after treatment of squamous cell cervical cancer can be offered hormone replacement therapy after discussing risks and benefits (IV, C). In patients with adenocarcinoma positive for oestrogen receptors, hormone replacement therapy could be offered on an individual basis after thorough discussion (III, C).

Ovarian cancer

Frequencies of follow-up after fertility-sparing management

Follow-up is recommended every 3–4 months for 2 years, every 6 months for another 3–5 years, and then annually for at least 10 years (IV, B). Follow-up should consist of physical examination and ultrasound examination by an experienced ultrasonographer (IV, B). Pelvic and abdominal CT or MRI should be performed at 6 months and then annually until the fifth year (IV, B). Measurement of cancer antigen-125 concentration or other tumour markers according to histotype (ie, inhibin B, anti-Müllerian hormone for sex cord stromal tumours, β-human chorionic gonadotrophin, α-fetoprotein, or lactate dehydrogenase for germ cell tumours) is only recommended when initially elevated or when presurgical markers are missing (IV, B). PET-CT is only indicated in cases of suspicion of recurrence (IV, B).

Surveillance during pregnancy

Transvaginal and abdominal ultrasonography should be performed by an experienced sonographer in early first and second trimester of pregnancy (IV, B). Follow-up of tumour markers is not recommended during pregnancy (IV, D). Breastfeeding is recommended as in the general population and should not be discouraged (IV, B).

Need for a completion surgery after childbearing

Routine completion surgery (removal of remaining ovary and tube) is not recommended in patients with borderline ovarian tumours (IV, D). Routine completion surgery is recommended in patients with a family history of genetic high-risk epithelial ovarian tumours (IV, B). Routine completion surgery could be considered on a case-by-case basis in patients with epithelial ovarian tumours (IV, C). Routine completion surgery is not recommended in patients with germ cell tumours (IV, D). In all other non-epithelial tumours, routine completion surgery could be offered on a case-by-case basis (IV, C). In patients with granulosa cell tumours, additional hysterectomy must be considered (IV, B).

Indications and modalities for hormone replacement therapy after completion surgery or bilateral salpingo-oophorectomy plus uterine preservation

Hormone replacement therapy can be offered after completion surgery to patients with borderline ovarian tumours and ovarian cancer after discussing risks and benefits and taking into account their histological subtype (IV, B).

Conclusion

Evidence-based guidelines were developed to help clinicians propose consensual management and harmonising treatments to try to give the best chances to patients with ovarian cancers, borderline ovarian tumours, or cervical cancers to become pregnant. These guidelines also provide recommendations for patient follow-up timelines after such treatment and when completion surgery is required. Multiplidisciplinary expertise is required for patients to preserve, when oncologically eligible, fertility potential during and after cancer treatment, including expertise from pathologists, radiologists, gynaecological oncologists, medical oncologists, radiation oncologists, and a strong collaboration and interaction with physicians specialising in assisted reproductive technologies. These evidence-based guidelines emphasise the crucial

Search strategy and selection criteria

A systematic, unbiased literature review of relevant studies published between Jan 1, 2003, and June 1, 2023, was carried out using MEDLINE, with search terms including but not limited to: "fatility-sparing surgery", "conservative surgery", "cervical cancer", "borderline ovarian tumour" and "ovarian cancer". The literature search was limited to publications in English. Priority was given to high-quality systematic reviews, meta-analyses, and randomised controlled trials, but studies of lower levels of evidence were also evaluated. We excluded editorials, letters, and in vitro studies. The reference list of each identified article was also reviewed for other potentially relevant articles. A list of abstracts from papers of potential interest was sent to the international development group, who then selected the full papers to be taken into account and could propose additional papers.

role of multidisciplinary methods, reflecting the need for centralisation of care in highly skilled teams to optimise the results of complex management of fertility-sparing treatments.

Contributors

The development group, which included all authors, is collectively responsible for the decision to submit for publication. PM, GS, MG, and FP wrote the first draft of the manuscript. All other contributors reviewed the manuscript and actively gave personal input and final approval before submission.

Declaration of interests

PM reports having had an advisory role or received speaker's honoraria (paid to him or to his institution) from GlaxoSmithKline, AstraZeneca, and ImmunoGen. GS reports grants or contracts from MSD, consulting fees from Tesaro Bio Italy and Johnson and Johnson, and payment or honoraria from Clovis Oncology Italy. NRA-R reports grants or contracts from Grail (paid to the institution). FFi reports honoraria from Theramex and Organon, and support for attending and travelling to meetings from Organon, Merck-Serono, and Theramex (paid to the institution). SB reports honoraria from MSD; support for attending and travelling to meetings from Hologic, MSD, and Pfizer; and honoraria for participation on a data safety monitoring board or advisory board from Hologic. CR-J reports payment for lectures (paid to the institution) from Organon and Novartis, speakers bureau (paid to the institution) from Gédéon Richter and Roche, and for manuscript writing (paid to the institution) from Roche. All other authors declare no competing interests.

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