Human Reproduction Open, pp. 1–17, 2020
doi:10.1093/hropen/hoaa052

human reproduction open

ESHRE PAGES

ESHRE guideline: female fertility preservation†

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Submitted on October 2, 2020; resubmitted on October 2, 2020; editorial decision on October 5, 2020

STUDY QUESTION: What is the recommended management for women and transgender men with regards to fertility preservation (FP), based on the best available evidence in the literature?

SUMMARY ANSWER: The ESHRE Guideline on Female Fertility Preservation makes 78 recommendations on organization of care, information provision and support, pre-FP assessment, FP interventions and after treatment care. Ongoing developments in FP are also discussed.

WHAT IS KNOWN ALREADY: The field of FP has grown hugely in the last two decades, driven by the increasing recognition of the importance of potential loss of fertility as a significant effect of the treatment of cancer and other serious diseases, and the development of the enabling technologies of oocyte vitrification and ovarian tissue cryopreservation (OTC) for subsequent autografting. This has led to the widespread, though uneven, provision of FP for young women.

STUDY DESIGN, SIZE, DURATION: The guideline was developed according to the structured methodology for development of ESHRE guidelines. After formulation of key questions by a group of experts, literature searches and assessments were performed. Papers published up to 1 November 2019 and written in English were included in the review.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Based on the collected evidence, recommendations were formulated and discussed until consensus was reached within the guideline group. A stakeholder review was organized after finalization of the draft. The final version was approved by the guideline group and the ESHRE Executive Committee.

MAIN RESULTS AND THE ROLE OF CHANCE: This guideline aims to help providers meet a growing demand for FP options by diverse groups of patients, including those diagnosed with cancer undergoing gonadotoxic treatments, with benign diseases undergoing gonadotoxic treatments or those with a genetic condition predisposing to premature ovarian insufficiency, transgender men (assigned

female at birth), and women requesting oocyte cryopreservation for age-related fertility loss.

The guideline makes 78 recommendations on information provision and support, pre-FP assessment, FP interventions and after treatment care, including 50 evidence-based recommendations—of which 31 were formulated as strong recommendations and 19 as weak—25 good practice points and 3 research only recommendations. Of the evidence-based recommendations, 1 was supported by high-quality evidence, 3 by moderate-quality evidence, 17 by low-quality evidence and 29 by very low-quality evidence. To support future research in the field of female FP, a list of research recommendations is provided.

LIMITATIONS, REASONS FOR CAUTION: Most interventions included are not well studied in FP patients. As some interventions, e.g. oocyte and embryo cryopreservation, are well established for treatment of infertility, technical aspects, feasibility and outcomes can be extrapolated. For other interventions, such as OTC and IVM, more evidence is required, specifically pregnancy outcomes after applying these techniques for FP patients. Such future studies may require the current recommendations to be revised.

WIDER IMPLICATIONS OF THE FINDINGS: The guideline provides clinicians with clear advice on best practice in female FP, based on the best evidence currently available. In addition, a list of research recommendations is provided to stimulate further studies in FP.

STUDY FUNDING/COMPETING INTEREST(S): The guideline was developed and funded by ESHRE, covering expenses associated with the guideline meetings, with the literature searches and with the dissemination of the guideline. The guideline group members did not receive payment. R.A.A. reports personal fees and non-financial support from Roche Diagnostics, personal fees from Ferring Pharmaceuticals, IBSA and Merck Serono, outside the submitted work; D.B. reports grants from Merck Serono and Goodlife, outside the submitted work; I.D. reports consulting fees from Roche and speaker's fees from Novartis; M.L. reports personal fees from Roche, Novartis, Pfizer, Lilly, Takeda, and Theramex, outside the submitted work. The other authors have no conflicts of interest to declare.

DISCLAIMER: *This guideline represents the views of ESHRE, which were achieved after careful consideration of the scientific evidence available at the time of preparation. In the absence of scientific evidence on certain aspects, a consensus between the relevant ESHRE stakeholders has been obtained. Adherence to these clinical practice guidelines does not guarantee a successful or specific outcome, nor does it establish a standard of care. Clinical practice guidelines do not replace the need for application of clinical judgment to each individual presentation, nor variations based on locality and facility type. ESHRE makes no warranty, express or implied, regarding the clinical practice guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. (Full disclaimer available at* www.eshre.eu/guidelines.*)*

[†]ESHRE Pages content is not externally peer reviewed. The manuscript has been approved by the Executive Committee of ESHRE.

Key words: fertility preservation / guideline / evidence-based / oncology / transgender men / age-related fertility loss / oocyte cryopreservation / ovarian tissue cryopreservation / ovarian transposition / pregnancy / organization of care

WHAT DOES THIS MEAN FOR PATIENTS?

Fertility preservation (FP) is a term used for interventions and procedures aiming at preserving the chance of having a baby when your fertility may be damaged by your medical condition or its treatment. FP may be appropriate before undergoing treatments that can affect fertility such as in women diagnosed with cancer or other non-malignant diseases (e.g. lupus, endometriosis and Turner syndrome). FP can also be considered by transgender men and by women worried about age-related fertility loss.

The current paper summarizes the ESHRE Guideline on FP providing clinicians with evidence-based recommendations on different FP techniques and how to apply them. These techniques include egg, embryo and ovarian tissue freezing, ovarian transposition and medical treatment to protect your ovaries. In addition, the guideline also provides recommendations on how to care for, inform and support patients requiring FP. The full guideline and a patient leaflet are available on https://www.eshre.eu/FFPguideline.

Introduction

The field of fertility preservation (FP) has grown hugely in the last two decades, driven by the increasing recognition of the importance of potential loss of fertility as a very important effect of the treatment of cancer and other serious diseases, and the development of the enabling technologies of oocyte vitrification and ovarian tissue cryopreservation for subsequent autografting. This has led to the widespread, though uneven, provision of FP for many women and young girls. The very rapid development of this field in clinical practice, yet with limited data on outcomes, has led to the need for the evaluation of the underpinning evidence and the development of guidelines to assist practitioners in its safe and effective implementation.

The guideline focuses on FP options for four populations: (i) post pubertal women diagnosed with cancer undergoing gonadotoxic treatments; (ii) post pubertal women with benign diseases undergoing gonadotoxic treatments or with conditions associated with premature loss of fertility, e.g. Turner syndrome; (iii) transgender men (assigned female at birth); and (iv) women considering oocyte cryopreservation for age-related fertility loss. In all these four populations, the guideline also provides recommendations regarding patient selection to ensure safe and effective care, including during future pregnancy. While it is recognized that this does not comprehensively include all those requiring FP (notably men, prepubertal girls and boys and transgender women), it was decided to limit the scope to focus primarily on adult women.

Materials and methods

The guideline was developed according to a well-documented methodology that is universal to ESHRE guidelines (Vermeulen et al., 2017). The guideline development group (GDG) was composed of past and present members of the coordination of the Special Interest groups (SIGs) Fertility Preservation and Quality and Safety in ART, with representation of other SIGs (SIG Psychology and counselling, and SIG Ethics and law), and addition of experts in the field, including oncologists, a scientist, and patient representatives.

In short, 21 key questions were formulated by the GDG, of which 7 were answered as narrative questions, and 14 as PICO (Patient, Intervention, Comparison, Outcome) questions. For each PICO question, databases (PUBMED/MEDLINE and the Cochrane library) were searched from inception to 1 November 2019, limited to studies written in English. From the literature searches, studies were selected based on the PICO questions, assessed for quality and summarized in evidence tables. GDG meetings were organized where the evidence and draft recommendations were presented by the assigned GDG member and discussed until consensus was reached within the group. Each recommendation was labelled as strong or weak and a grade was assigned based on the strength of the supporting evidence (High ⊕⊕⊕⊕, Moderate ⊕⊕⊕◯, Low ⊕⊕◯◯, Very low ⊕◯◯◯). Good practice points (GPPs) based on clinical expertise were added where relevant to clarify the recommendations or to provide further practical advice. 'Research only' recommendations were also made, and those interventions should be applied only within the context of research, with appropriate precautions and ethical approval.

Strong recommendations should be used as a recommendation to be applied for most patients, while weak recommendations require discussion and shared decision-making.

For the narrative questions, a similar literature search was conducted. Collected data were summarized in a narrative summary and conclusions were formulated.

The guideline draft and an invitation to participate in the stakeholder review were published on the ESHRE website between 6 May and 17 June 2020. All comments were processed by the GDG, either by adapting the content of the guideline and/or by replying to the reviewer. The review process was summarized in the review report which is published on the ESHRE website (www.eshre.eu/Guidelines). Overall, 71.5% of the 231 comments resulted in an adaptation or correction in the guideline text.

This guideline will be considered for update 4 years after publication, with an intermediate assessment of the need for updating 2 years after publication.

Results

Key questions and recommendations

The current document summarizes all the key questions and the recommendations from the guideline 'Female Fertility Preservation'. Further background information and the supporting evidence for each recommendation can be found in the full version of the guideline available at https://www.eshre.eu/FFPguideline.

Organization of care

How should the care for women undergoing fertility preservation be organized?

A team approach to care for women undergoing FP is advocated in the guideline. To support implementation, the following suggestions were formulated (Figure 1).

There should be agreement within an FP service for who is responsible for all issues, including agreement on referral pathways, availability of standard forms for diagnosis, intended therapy, time intervals and a check whether FP counselling has been offered and has taken place. For FP treatment, a member of the FP team should be responsible for discussing any proposed treatment with the clinical care team before treatment initiation. Documentation and registration should be organized; all relevant medical information should be documented in the patients' medical records, all patients undergoing FP should have been counselled about the legal and financial consequences and must have given written informed consent and accurate supporting documentation, especially about the gametes/embryos/tissue stored, is essential as storage may last for many years.

A direct link between the clinical care team and the FP team, preferably in multidisciplinary team meetings, is recommended. In addition, identification of a key individual (the 'coordinator') in clinical care teams is advisable to facilitate patients of reproductive age meeting with the FP team. Psychological support/counselling should be available to all patients considering FP, and specific support for particular patient groups may be required.

Expanding access to FP options is also important in the organization of FP care. The guideline group advocates improving (i) public awareness of fertility and of factors that may have negative effects on it; (ii) oncologists' awareness of FP options; (iii) referral pathways; and (iv) availability of different FP procedures. With regard to these items, specific attention should be given to FP care for specific patient groups, such as adolescents and transgender men.

The key organizational features for establishing an FP program are summarized in Figure 2.

With regard to availability of FP interventions and storage of reproductive material, a survey was conducted to collect national legislative information in European countries, while recognizing that this is a constantly changing area. It was concluded that FP is available in most but not all European countries; thus, specialists should be aware of their national legislative and regulatory situation. This generally supportive legislative environment applies to patients with cancer and benign diseases, and mostly to transgender men. Provision of financial support is less widespread. This may reflect the rapidly developing nature of some FP procedures, and the ongoing change in their status from experimental towards being part of established care. With regards to the duration of storage of reproductive materials, regulations are very variable across Europe. Some countries also have different storage regulations for different materials. While a duration of storage is often applied, this may be supplemented by an upper age limit for use. Given the young age at which FP may occur, the often short allowable duration of storage (5–10 years in many countries) is inappropriate, and legislation should focus more on a maximum age of use.

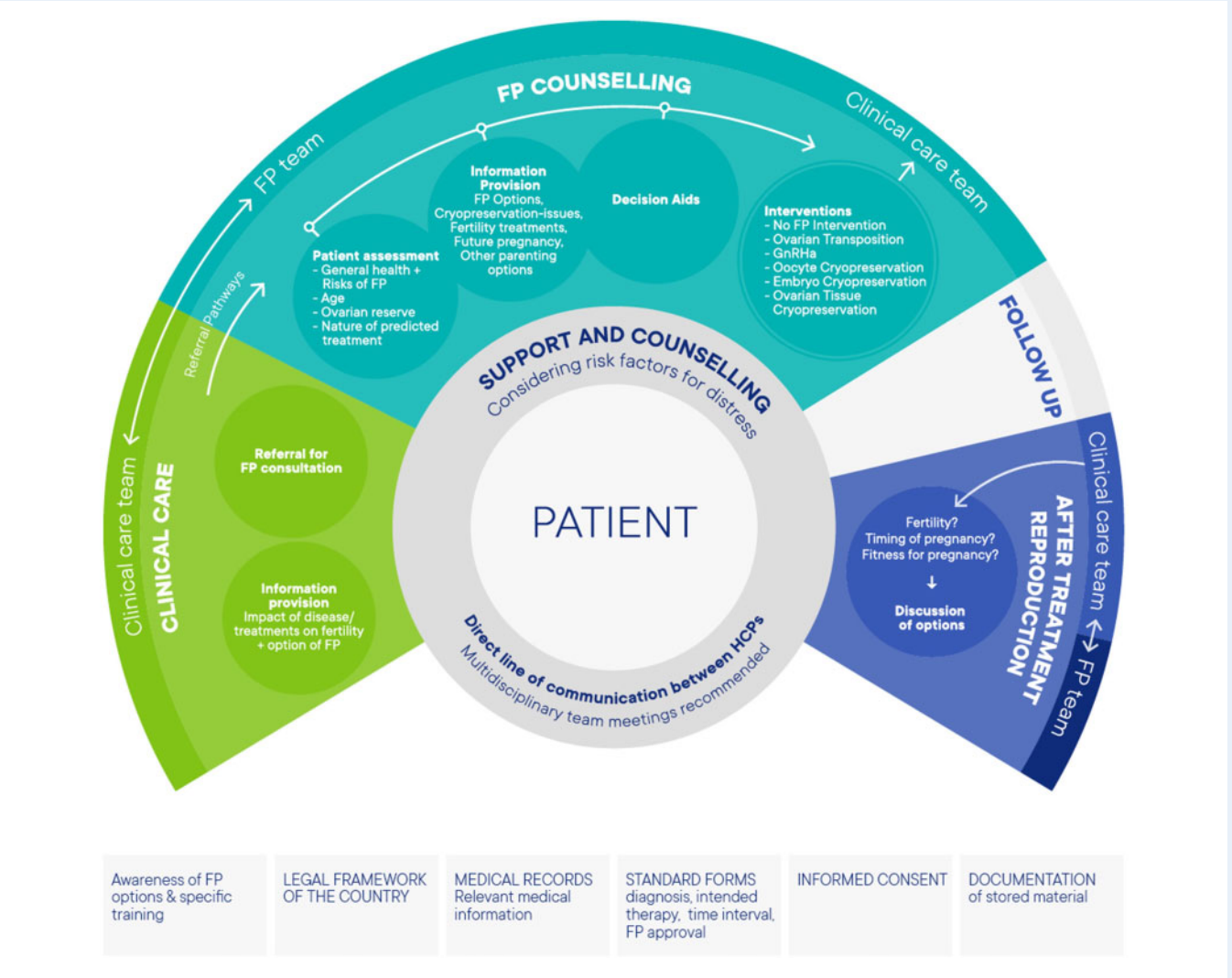

Figure 1. Model of care for patients eligible for fertility preservation (FP).

Information needs and provision

What information needs to be provided to women at risk of infertility?

Clinicians should provide information to patients regarding (i) impact of cancer, other diseases and their treatments on reproductive function; (ii) impact of cancer, other diseases and their treatment on fertility, (iii) FP options; (iv) issues related to cryopreservation storage after FP, (v) infertility and fertility treatments; (vi) pregnancy after gonadotoxic treatment or underlying condition; and (vii) other childbearing and parenting options (Peate *et al.*, 2009; Goossens *et al.*, 2014; Silva *et al.*, 2018) (see Supplementary data I for more details).	STRONG ⊕⊕◯◯
Information provided should be specific to the patients' needs.	GPP
Age-specific information and counselling should be provided for adolescents and young adults.	GPP

How should information on fertility preservation options be provided to patients?

It is recommended to provide decision aids to patients who are considering FP (Peate *et al.*, 2009; Anazodo *et al.*, 2019; Wang *et al.*, 2019).	STRONG ⊕⊕◯◯
Healthcare professionals may consider the use of a checklist for a better provision of information to patients (Kemertzis *et al.*, 2018).	WEAK ⊕◯◯◯

The full guideline includes a table of decision aids that are currently available for FP interventions. A checklist for clinicians to cover the information needs of patients undergoing FP counselling (for the four different indications) is included as Supplementary data I.

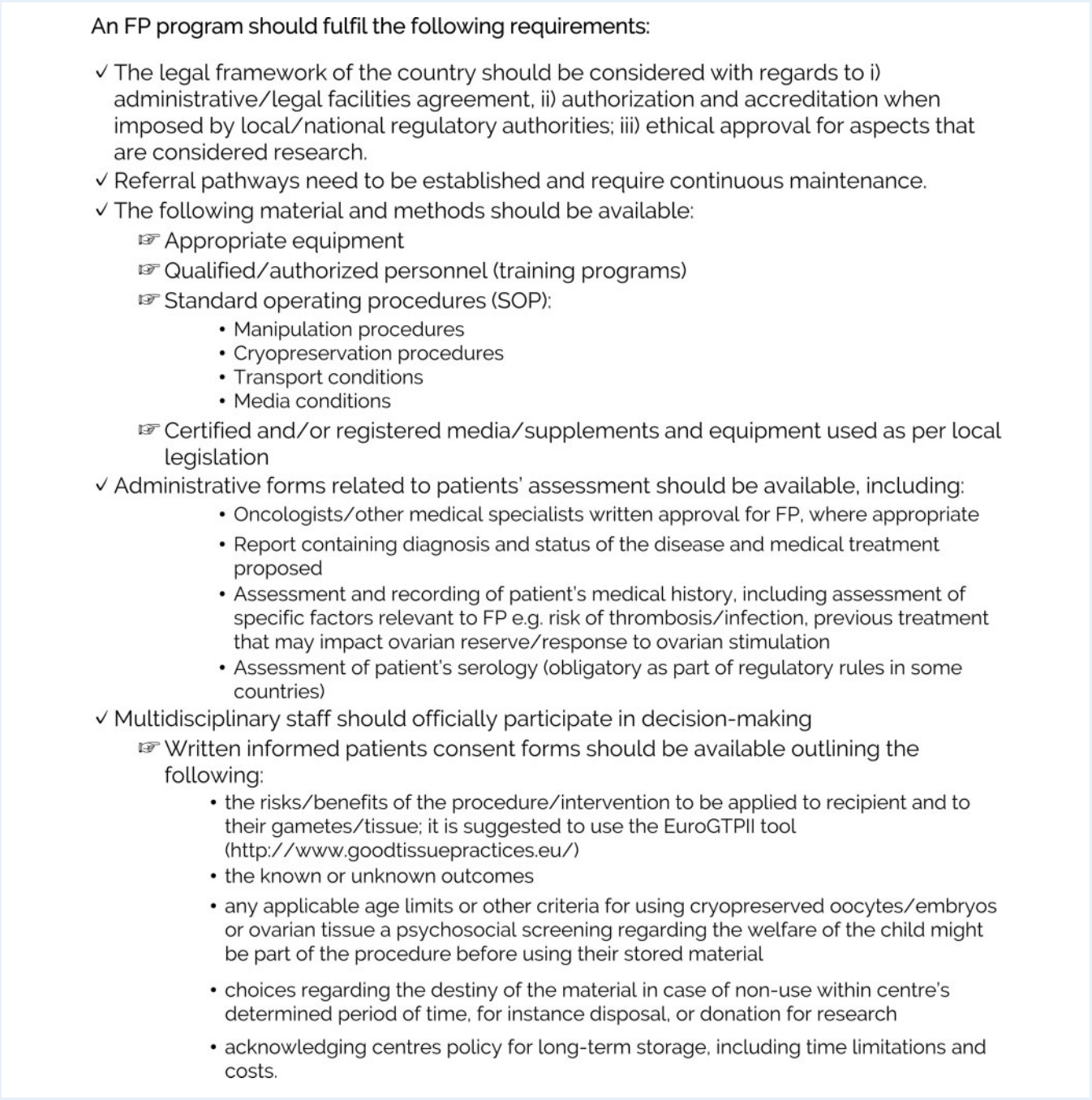

Figure 2. Checklist for a high-quality fertility preservation (FP) program.

Is there a benefit of psychological support and counselling and are there particular groups that would benefit from it?

It is recommended that patients are offered psychological support and counselling when dealing with FP decisions, although the extent of the clinical benefit has not been studied (Chiavari *et al.*, 2015; Greenwood *et al.*, 2018; Logan *et al.*, 2018; Anazodo *et al.*, 2019).

STRONG ⊕○○○

The multidisciplinary FP team counselling FP patients should be aware that maladaptive psychological processes and past psychopathology are risk factors for psychological distress during FP decision. It is recommended that patients at risk are referred for psychological support when needed.

Clinicians may consider referring FP patients who present risk factors for psychological distress for psychological support and counselling (Lawson *et al.*, 2014; O'Hea *et al.*, 2016; Shah *et al.*, 2016; Witcomb *et al.*, 2018; Logan *et al.*, 2019).

WEAK ⊕○○○

Patient selection and pre-FP assessment

Which criteria can be used to select patients for fertility preservation?

Patients require an individual assessment of the indications and risks prior to FP interventions.	GPP
A multidisciplinary team is recommended to have an accurate assessment of risks.	GPP
For women with overt premature ovarian insufficiency (POI), FP is not recommended.	GPP

A checklist for patient assessment and selection for FP is presented in Figure 3.

Which factors should be taken into account when estimating the individual risk of gonadotoxicity for a patient?

The risk of gonadotoxicity should be assessed in all patients undergoing gonadotoxic treatments.	GPP
To estimate the individual risk of gonadotoxicity, the characteristics of the proposed treatment, the patient and the disease should be considered (Tauchmanova *et al.*, 2003; Bernhard *et al.*, 2007; Anderson and Cameron, 2011; Abusief *et al.*, 2012; Lawrenz *et al.*, 2012; van der Kaaij *et al.*, 2012; Valentini *et al.*, 2013; Akhtar *et al.*, 2015; Ruddy *et al.*, 2015; Lekovich *et al.*, 2016; Silva *et al.*, 2016; Freour *et al.*, 2017; Lambertini *et al.*, 2017, 2019a,d; Dezellus *et al.*, 2017a; Anderson *et al.*, 2017b,c).	STRONG ⊕⊕◯◯

An overview of factors that increase the risk of gonadotoxicity, and of factors where evidence is not yet available in presented in Figure 4.

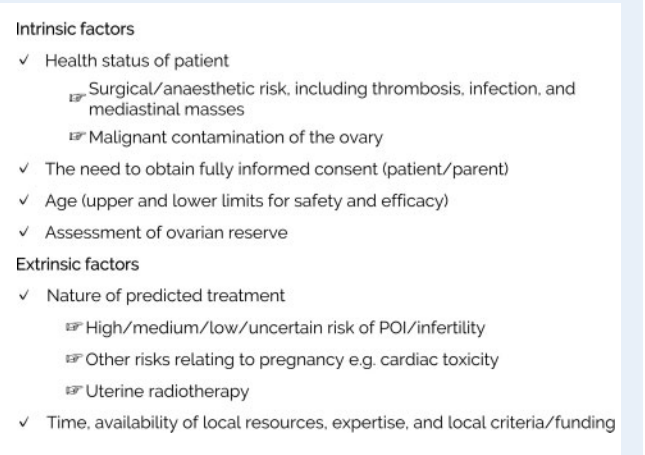

Figure 3. Checklist for patients' assessment and selection for fertility preservation (FP) interventions (adapted from Wallace *et al.* (2012)).

Is it relevant to do ovarian reserve testing, and for whom?

For predicting high and low response to ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests.	STRONG ⊕⊕◯◯
Assessment of pre-treatment ovarian function, in particular through AMH levels, in premenopausal women with a diagnosis of breast cancer or haematological malignancy is recommended to predict post-treatment recovery of ovarian function (Anderson *et al.*, 2013; Dillon *et al.*, 2013; Peigne and Decanter, 2014; Su *et al.*, 2014; Silva *et al.*, 2016; Dezellus *et al.*, 2017b).	STRONG ⊕⊕◯◯
Pre-treatment AMH levels should not be used as an indicator of post-treatment fertility (Hamy *et al.*, 2016).	WEAK ⊕◯◯◯
When estimating the risk of post-treatment POI, age, proposed gonadotoxic treatment type and dose, as well as pre-treatment AMH levels, should be taken into consideration (Anderson *et al.*, 2013; Su *et al.*, 2014; Barnabei *et al.*, 2015).	STRONG ⊕◯◯◯
Pre-treatment ovarian reserve testing could be performed in women with other malignancies, as testing is likely to be of high relevance based on indirect evidence from breast and haematological cancers (Dillon *et al.*, 2013).	WEAK ⊕◯◯◯
The relevance of ovarian reserve testing to help guide FP options or treatment decisions in systemic lupus erythematosus patients is low (Morel *et al.*, 2013).	WEAK ⊕◯◯◯
The relevance of ovarian testing to help guide FP options or treatment decisions in endometriosis patients remains inconclusive (Reinblatt *et al.*, 2011; Benaglia *et al.*, 2013; Ashrafi *et al.*, 2019; Zhou *et al.*, 2019).	WEAK ⊕◯◯◯
Clinicians should be aware that in patients with endometriosis, the involvement of the ovaries and the radicality of surgery influence ovarian reserve as measured by AMH levels, but that its relevance to future fertility is unclear.	GPP
For women with reduced ovarian reserve (Bologna criteria, AMH <0.5 ng/ml), advice needs to be individualized and the value of FP is unclear.	GPP

Fertility preservation interventions

Which options are available for fertility preservation in women—emergency and non-emergency?

Fertility can be preserved through several procedures, including cryopreservation of oocytes, embryos or ovarian tissue, and potentially medical and surgical methods of protection (see Figure 5). Since the development of vitrification, oocyte cryopreservation is the method of choice for women undergoing treatment for age-related fertility loss, and for most women undergoing FP for medical indications. Embryo cryopreservation is even more widely available and long-established part of assisted reproduction, but the necessity for joint legal ownership with the male partner is an important consideration that may result in difficulties later on. Ovarian tissue cryopreservation (OTC) is an important option either through choice, or if there is insufficient time for ovarian stimulation. *In vitro* oocyte maturation (IVM) can also be considered, and in some cases, there may be a possibility of combining different approaches.

Protection of the ovary against the effects of treatment would be an ideal approach. Options include GnRH agonists (mostly investigated in women with breast cancer) and ovarian transposition in women scheduled for pelvic radiotherapy.

Figure 4. Summary of factors to be considered when estimating the risk of gonadotoxicity.

How should ovarian stimulation be performed in cancer patients undergoing FP treatment?

For ovarian stimulation in women seeking FP for medical reasons, the GnRH antagonist protocol is recommended for its feasibility in urgent situations, short time and safety reasons (The ESHRE Guideline Group on Ovarian Stimulation *et al.*, 2020).	STRONG ⊕◯◯◯
For patients requiring ovarian stimulation where there is a lack of urgency, the use of a long protocol may also be appropriate (The ESHRE Guideline Group on Ovarian Stimulation *et al.*, 2020).	WEAK ⊕◯◯◯
In urgent FP cycles, random-start ovarian stimulation is an option (Marklund *et al.*, 2020; The ESHRE Guideline Group on Ovarian Stimulation *et al.*, 2020).	WEAK ⊕⊕◯◯
Double stimulation can be considered for urgent FP cycles (The ESHRE Guideline Group on Ovarian Stimulation *et al.*, 2020; Vaiarelli *et al.*, 2020).	WEAK ⊕⊕◯◯
In ovarian stimulation for FP in oestrogen-sensitive diseases the concomitant use of anti-oestrogen therapy, such as letrozole, is probably recommended.	GPP
For ovarian stimulation in transgender men aiming at oocyte cryopreservation, GnRH antagonist protocols can be considered as they have been shown to be feasible and with numbers of oocytes retrieved comparable to those obtained in cisgender women when individuals have stopped previous treatment with testosterone.	WEAK ⊕◯◯◯

How should ovarian stimulation be performed in transgender men undergoing FP treatment?

For transgender men, the addition of letrozole to the antagonist protocol can be considered as it may enhance treatment adherence by reducing oestrogenic symptoms (Armuand et al., 2017).	GPP

Is oocyte cryopreservation effective and safe for FP?

Oocyte cryopreservation should be offered as an established option for FP (Rienzi *et al.*, 2012; Cobo *et al.*, 2013; Druckenmiller *et al.*, 2016; Massarotti *et al.*, 2017; Cobo *et al.*, 2018; Rodriguez-Wallberg *et al.*, 2019b).	STRONG ⊕⊕◯◯
Women with a partner should be offered the option to cryopreserve unfertilized oocytes or to split the oocytes to attempt both embryo and oocyte cryopreservation.	GPP
Women should be informed of accurate, centre-specific expertise and live birth rates. They should also be informed that success rates after cryopreservation of oocytes at the time of a cancer diagnosis may be lower than in women without cancer.	GPP

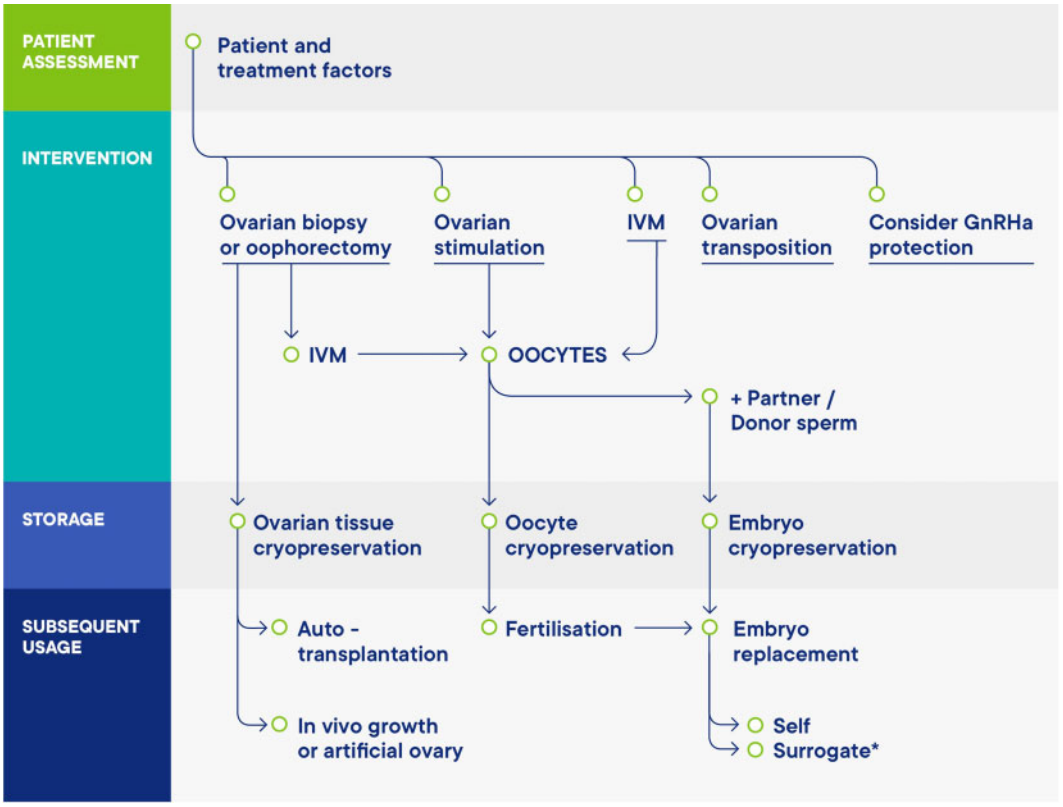

Figure 5. Schematic overview of the options for female fertility preservation (FP). Adapted from (Anderson *et al.*, 2015) .

Oocyte cryopreservation for age-related fertility loss

Women considering oocyte cryopreservation for age-related fertility loss should be fully informed regarding the success rates, risks, benefits, costs and the possible long-term consequences, both in terms of physical and psychological health (Rienzi *et al.*, 2012; Cobo *et al.*, 2013; Druckenmiller *et al.*, 2016; Massarotti *et al.*, 2017; Cobo *et al.*, 2018; Ethics Committee of the American Society for Reproductive Medicine, 2018; Rodriguez-Wallberg *et al.*, 2019b; Anderson *et al.*, 2020). — STRONG ⊕◯◯◯

Suitability should be determined on a case-by-case basis. — GPP

Is embryo cryopreservation effective and safe for fertility preservation?

Embryo cryopreservation is an established option for FP (Dolmans *et al.*, 2005; Barcroft *et al.*, 2013; Courbiere *et al.*, 2013; Debrock *et al.*, 2015; Dolmans *et al.*, 2015; Rienzi *et al.*, 2017; Alvarez and Ramanathan, 2018; Cobo *et al.*, 2018; Rodriguez-Wallberg *et al.*, 2019a). — STRONG ⊕⊕◯◯

Women should be informed about the risk of losing reproductive autonomy and possible issues with ownership of stored embryos. — GPP

Women should be informed of accurate, centre-specific expertise and live birth rates. They should also be informed that success rates after cryopreservation of embryos at the time of a cancer diagnosis may be lower than in women without cancer. — GPP

Should ovarian tissue cryopreservation be used for FP?

It is recommended to offer OTC in patients undergoing moderate/high-risk gonadotoxic treatment where oocyte/embryo cryopreservation is not feasible, or at patient preference (Pacheco and Oktay, 2017; Gellert *et al.*, 2018). — STRONG ⊕⊕◯◯

OTC should probably not be offered to patients with low ovarian reserve (AMH < 0.5 ng/ml and AFC < 5) or advanced age considering the unfavourable risk/benefit. Current evidence suggest that the efficiency of OTC procedure is questionable above 36 years of age (Paradisi *et al.*, 2016; Diaz-Garcia *et al.*, 2018; Gellert *et al.*, 2018). — WEAK ⊕◯◯◯

The GDG considers that OTC is an innovative method for ovarian function and fertility preservation in post pubertal women. — GPP

Patients who have already received low gonadotoxic treatment or a previous course of chemotherapy, can be offered OTC as FP option (Poirot *et al.*, 2019). — WEAK ⊕◯◯◯

Ovarian stimulation can be performed immediately after OTC (Huober-Zeeb *et al.*, 2011; Dittrich *et al.*, 2013; Dolmans *et al.*, 2014). — WEAK ⊕◯◯◯

OTC at the time of oocyte pick-up after ovarian stimulation should not be performed unless in a research context. — RESEARCH ONLY

Ovarian transposition can be performed at the same time as OTC in patients who will receive pelvic irradiation. — GPP

OTC is not recommended as the primary FP procedure in transgender men but can be proposed as an experimental option when ovaries are removed during gender reassignment surgery. — GPP

OTC/ovarian tissue transplantation (OTT) can be considered in patients with POI-associated genetic and chromosomal disorders but requires genetic counselling and should be performed within a research protocol.	RESEARCH ONLY

Should vitrification versus slow-freezing be used for OTC for FP?

The slow-freezing protocol should be used for OTC as it is well-established and considered as standard (Fabbri *et al.*, 2016; Dalman *et al.*, 2017; Shi *et al.*, 2017).	STRONG ⊕◯◯◯
Vitrification of ovarian tissue should only be offered within a research program.	RESEARCH ONLY

Which safety issues should be considered when replacing ovarian tissue?

For OTT, a one-step laparoscopy procedure should be performed as it is considered safe without causing additional surgical risk (Schmidt *et al.*, 2011; Beckmann *et al.*, 2017, 2018).	STRONG ⊕⊕◯◯
OTT at the orthotopic site is recommended to restore fertility (Beckmann *et al.*, 2017; Gellert *et al.*, 2018).	STRONG ⊕⊕◯◯
The decision to perform OTT in oncological patients requires a multidisciplinary approach.	GPP
It is recommended to evaluate the presence of residual neoplastic cells in the ovarian cortex (and in the residual medulla when available) using appropriate techniques in all cancer survivors before OTT and patients should be informed about this risk (Abir *et al.*, 2010; Bittinger *et al.*, 2011; Fabbri *et al.*, 2012; Greve *et al.*, 2012; Bastings *et al.*, 2013; Dolmans *et al.*, 2013, 2016; Jahnukainen *et al.*, 2013; Luyckx *et al.*, 2013; Bockstaele *et al.*, 2015; Rodriguez-Iglesias *et al.*, 2015; Kristensen *et al.*, 2017; Anderson *et al.*, 2017d; Andersen *et al.*, 2018; Gellert *et al.*, 2018; Masciangelo *et al.*, 2018; Shapira *et al.*, 2018).	STRONG ⊕◯◯◯
OTT is not recommended in cases where the ovary is involved in the malignancy (Kristensen *et al.*, 2017; Masciangelo *et al.*, 2018).	STRONG ⊕◯◯◯
OTT and pregnancy can be considered in hormone-sensitive tumours such as endometrial cancer treated by fertility-sparing strategy or breast cancer, after complete remission of the disease (Lambertini *et al.*, 2018a).	STRONG ⊕⊕◯◯
There appears to be no increased risk of congenital abnormalities for children born after OTT (Pacheco and Oktay, 2017; Gellert *et al.*, 2018).	WEAK ⊕◯◯◯
Long-term risks in human are considered to be low but a long-term follow-up of patients after OTT is recommended.	GPP
OTT can be offered in BRCA patients, as an alternative when egg or embryo freezing is not feasible, but the ovarian tissue must be completely removed after subsequent pregnancy (Lambertini *et al.*, 2018a, 2019b).	WEAK ⊕◯◯◯

Should IVM be used for FP?

IVM should be regarded as an innovative FP procedure (Moria *et al.*, 2011; Creux *et al.*, 2018; Grynberg *et al.*, 2019).	STRONG ⊕◯◯◯
IVM requires specific expertise and should only be performed when oocyte cryopreservation is required but ovarian stimulation not feasible.	GPP
IVM after *ex vivo* extraction can be offered as an experimental procedure.	WEAK ⊕◯◯◯

Should GnRH agonists be used for ovarian protection in patients undergoing gonadotoxic treatment?

GnRH agonists during chemotherapy should be offered as an option for ovarian function protection in premenopausal breast cancer patients receiving chemotherapy; however, limited evidence exists on their protective effect on the ovarian reserve and the potential for future pregnancies (Lambertini *et al.*, 2015, 2018c).	STRONG ⊕⊕⊕⊕
In women with breast cancer, GnRH agonists during chemotherapy should not be considered an option for FP instead of cryopreservation techniques (Lambertini *et al.*, 2015, 2018c).	STRONG ⊕⊕⊕◯
In malignancies other than breast cancer, GnRH agonists should not be routinely offered as an option for ovarian function protection and FP without discussion of the uncertainty about its benefit (Gilani *et al.*, 2007; Senra *et al.*, 2018).	STRONG ⊕◯◯◯
GnRH agonists during chemotherapy may be considered as an option for ovarian function protection in premenopausal patients with autoimmune diseases receiving cyclophosphamide. However, it should be acknowledged that limited data are available in this setting (Ben-Aharon *et al.*, 2010; Marder *et al.*, 2012; Brunner *et al.*, 2015).	WEAK ⊕⊕◯◯
GnRH agonists should not be considered an equivalent or alternative option for FP but can be offered after cryopreservation techniques or when they are not possible.	GPP

Should transposition of ovaries be used for ovarian protection?

Where pelvic radiotherapy without chemotherapy is planned, women may be offered ovarian transposition with the aim to prevent POI (Gubbala *et al.*, 2014; Hoekman *et al.*, 2019).	WEAK ⊕⊕◯◯
Women with reduced ovarian reserve and women at risk of having ovarian metastases are inappropriate candidates for ovarian transposition.	GPP

After treatment care

How should patients be re-assessed before use of stored material?

Before the use of stored material, fitness for pregnancy should be thoroughly assessed, taking into account treatment late effects, the age of the patient and the interval since treatment.	STRONG ⊕◯◯◯
The need for psychological counselling, pre-conception counselling and fertility treatment counselling should be considered for all patients. Local guidelines for counselling should be followed.	GPP

Information on patient re-assessment before attempting pregnancy (with or without the use of stored material) is summarized in Figure 6. With regards to pre-conception counselling, a checklist was prepared outlining the reproductive options after FP for cancer patients and for transgender men (Supplementary data II).

What is the effect of previous gonadotoxic treatments and underlying conditions on obstetric outcomes?

Preconception counselling and appropriate obstetric monitoring is recommended in women intending to become pregnant after gonadotoxic treatments (Fossa *et al.*, 2005; Madanat-Harjuoja *et al.*, 2013; Ji *et al.*, 2016; Anderson *et al.*, 2017a; van der Kooi *et al.*, 2018).	STRONG ⊕⊕⊕◯
An interval of at least 1 year following chemotherapy completion is suggested before attempting a pregnancy in order to reduce the risk of pregnancy complications (Hartnett *et al.*, 2018).	STRONG ⊕◯◯◯
Radiotherapy to a field that included the uterus increases the risk of pregnancy complications; this risk is age (higher at prepubertal ages) and dose dependent. These pregnancies should be treated as high risk and managed in a centre with advanced maternity services (Sanders *et al.*, 1996; Critchley and Wallace, 2005; Signorello *et al.*, 2010; Teh *et al.*, 2014; Tarin *et al.*, 2016; van de Loo *et al.*, 2019).	STRONG ⊕◯◯◯
After completion of the recommended treatment, pregnancy is safe in women who have survived breast cancer. This is independent of oestrogen receptor status of the tumour (Hartman and Eslick, 2016; Sun *et al.*, 2018; Lambertini *et al.*, 2018b; Lee *et al.*, 2019; Schuurman *et al.*, 2019).	STRONG ⊕⊕◯◯
Pregnancy after treatment for breast cancer should be closely monitored, as there is an increased risk of preterm birth and low birth weight. Patients should be informed about these risks (Hartman and Eslick, 2016; Sun *et al.*, 2018; Lee *et al.*, 2019; Schuurman *et al.*, 2019; Lambertini *et al.*, 2019c).	STRONG ⊕⊕⊕◯
Reliable non-hormonal contraception is mandatory during tamoxifen treatment. It is recommended to stop tamoxifen for at least 3 months before attempting pregnancy.	GPP
Women with endometrial cancer should be followed up for high-risk pregnancy and monitored by an oncologist due to the risk of relapse (Chao *et al.*, 2011; Park *et al.*, 2013).	STRONG ⊕◯◯◯
The risk of preterm birth is increased after treatment for early cervical cancer and these pregnancies should be treated as high risk and managed in a centre with advanced maternity services (Bentivegna *et al.*, 2016; Kyrgiou *et al.*, 2017; Zhang *et al.*, 2017).	STRONG ⊕⊕◯◯
Women previously treated for cancer require individual assessment of their obstetric risks and potential additional obstetric surveillance (Longhi *et al.*, 2000; do Rosario *et al.*, 2006; Haggar *et al.*, 2013; Marklund *et al.*, 2018).	STRONG ⊕◯◯◯
Healthcare professionals should have a high level of awareness of the risk of depression and increased dysphoria during and after pregnancy care for transgender men (Light *et al.*, 2014; Obedin-Maliver and Makadon, 2016; Brandt *et al.*, 2019).	WEAK ⊕◯◯◯

With regards to obstetric outcomes after oocyte cryopreservation for age-related fertility loss, it has been shown that there are risks of due to older age at pregnancy, which increase after the age of 45 (Aoyama *et al.*, 2019). More research is needed on the number of women who return to use their frozen oocytes, pregnancy complications, and live birth rates in these women.

Future FP interventions

What are ongoing developments with regards to FP?

To increase the spectrum of FP options, innovative technologies and novel *in vitro* avenues are continually being developed. This includes technologies involving transplantation into the patient, such as transplantation of the whole ovary after cryopreservation and procedures to optimize the use of transplanted ovarian cortex tissue, such as *in vitro* activation, processes to reduce ischaemia by promoting revascularization, techniques to eliminate residual malignant cells, methods for transplantation of follicles isolated from ovarian cortex tissue as bioprosthetic ovaries, and methods for transplantation of isolated cells into the remaining (gonadotoxic-exposed) ovary. Another line of research focuses on technologies that do not involve transplantation, such as *in vitro* matured oocytes from cultured ovarian cortex tissue, *in vitro* matured oocytes from primordial follicles isolated from ovarian cortex tissue and *in vitro* matured oocytes from cells isolated from the ovary. In addition, research is conducted in the use of *in vitro* matured oocytes from induced pluripotent stem cells (*in vitro* gametogenesis) or from mesenchymal stromal cells. Treatments to prevent gonadotoxic-induced POI have been recently reviewed (Spears *et al.*, 2019).

Regarding future FP interventions, the GDG formulated the following conclusion: It is important to stress that emerging technologies, however promising, need to be followed by rigorous clinical trials, ensuring internationally accepted standards, to demonstrate efficacy and safety before they can be offered as medical treatment. Moreover, a scientific-medical consensus is required regarding safety and functional criteria that needs to be achieved before considering clinical use of *in vitro*-derived human oocytes. In this regard, a societal debate on the ethical issues and what emerging technologies may be considered acceptable for human reproductive purposes is recommended.

Discussion

The current paper summarizes the 78 recommendations on information provision and support, pre-FP assessment, FP interventions and after treatment care from the ESHRE Guideline on 'Female Fertility Preservation'. This Guideline covers all aspects of FP on four different patient populations, specifically cancer patients, patients with benign diseases, transgender men and women requesting FP for age-related fertility loss, and was written by a multidisciplinary group with gynaecologists and fertility specialists, oncologists, a psychologist, a bioethicist, an embryologist, a scientist, and patient representatives.

According to the World Health Organization, individuals and couples have the right to decide the number, timing and spacing of their children (https://www.who.int/news-room/fact-sheets/detail/infertility). FP can be considered one option in preventing infertility and an important part of realizing the right to have a family. The importance of FP has also been demonstrated at the start of the COVID-19 pandemic, when ESHRE recommended not starting fertility treatments with the exception of treatments for FP. It has been shown that although most fertility treatments were suspended, FP interventions were continued in most centres throughout Europe (Vermeulen *et al.*, 2020).

Notwithstanding the importance and relevance of FP, research data on many aspects are scarce. As a basis for the current guideline, a broad and formal literature review was conducted. Few relevant RCTs have been performed, with evidence for most interventions deriving from case series. Research gaps were detected in several areas, and these are documented in a list of recommendations for further research (Supplementary data III). Although the literature searches focused on the four patient populations separately, most studies

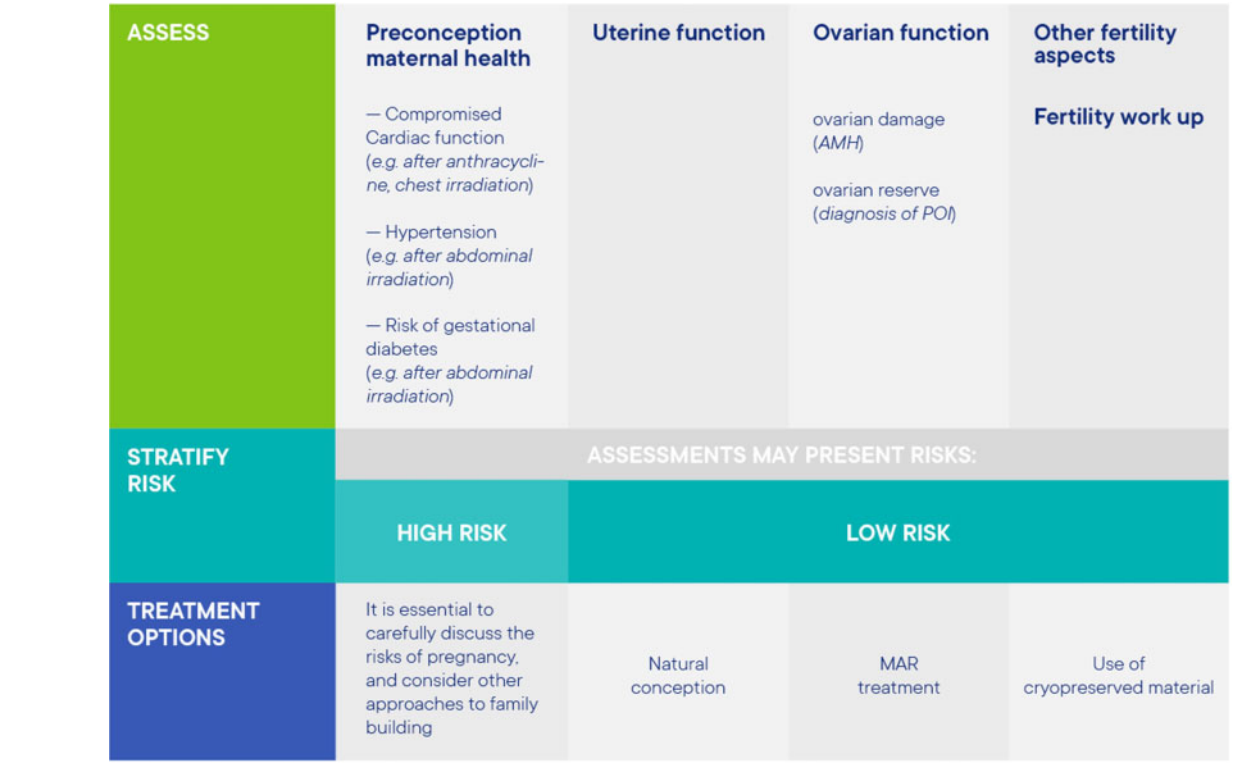

Figure 6. Patient re-assessment before attempting pregnancy (with or without the use of stored material).

included in the guideline reported on women with cancer, mostly breast cancer, with very few studies on FP in benign diseases, and even fewer on FP in transgender men and in women requesting FP for age-related fertility loss. For the latter patient groups, most reports focus on feasibility, acceptability and ethical considerations, rather than efficacy, efficiency and safety. To advance the field of female FP, more research is needed on the efficacy and safety of both established and newer techniques with a focus on achievement of live birth, but also on patient preferences and indications for FP. Indeed, one key aspect of the provision of FP is the need to widen access, while offering it to appropriately selected patients with a relevant indication. The variable provision of FP interventions deprives some women from having a family. However, applying FP to all patients undergoing gonadotoxic treatment, even with limited gonadotoxicity, will result in large amounts of stored but unused reproductive cells and tissue, creating unnecessary burden and costs for some patients involved and for health services. The risk of gonadotoxicity can be estimated or quantified in those patients receiving specific treatments that have been studied in sufficient detail, albeit generally with ovarian reserve testing which has very limited value for predicting future fertility. For many patients, the risk and benefits of FP interventions require multidisciplinary discussion and decision-making with regards to FP. New targeted treatments in oncology including immunotherapy largely have unknown gonadotoxicity (Lambertini *et al.*, 2020). Providing appropriate information to patients and supporting their decision-making is crucial, both on whether to proceed with FP, and when it has become time to attempt pregnancy. Patient information leaflets summarizing the guideline's most relevant information for patients are available and can be used as a template, and links to decision aids are provided.

Despite the limitations of guidelines in general, and the limitations in the evidence supporting the current guideline, the guideline group is confident that this document will help best practice in female FP.

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

Acknowledgements

The Guideline Development Group would like to acknowledge the help of many clinicians and professional organizations who refereed the content of the Guideline and submitted helpful comments to the draft version.

Authors' roles

R.A.A. chaired the GDG and hence fulfilled a leading role in collecting the evidence, writing the manuscript and dealing with reviewer comments. N.V., as methodological expert, performed all literature searches for the guideline, provided methodological support and coordinated the guideline development. S.D. and C.M. represented the patient perspective in the guideline group. All other authors, listed in

alphabetical order, as GDG members, contributed equally to the manuscript, by drafting key questions, synthesizing evidence, writing the different parts of the guideline and discussing recommendations until consensus within the group was reached.

Funding

The study has no external funding; all costs for meetings were covered by ESHRE.

Conflict of interest

R.A.A. reports personal fees and non-financial support from Roche Diagnostics, personal fees from Ferring Pharmaceuticals, IBSA and Merck Serono, outside the submitted work; D.B. reports grants from Merck Serono and Goodlife, outside the submitted work; I.D. reports consulting fees from Roche and speaker's fees from Novartis; M.L. reports personal fees from Roche, Novartis, Pfizer, Lilly, Takeda and Theramex, outside the submitted work. The other authors have no conflicts of interest to declare.

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