Critical Reviews in Oncology / Hematology 138 (2019) 233–240

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

EUropean REcommendations for female FERtility preservation (EU-REFER): A joint collaboration between oncologists and fertility specialists

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ARTICLE INFO

Keywords:
Oncofertility
Female cancer patients
Fertility preservation
Expert recommendations
Oncologists
Haematologists

ABSTRACT

In recent years, following the improved prognosis of patients with cancer, interest and attention has grown around fertility issues in these patients. International guidelines on fertility preservation in patients with cancer recommend that physicians discuss with all patients of reproductive age (or their parents/guardians, if children) the risk of infertility arising from their cancer or its treatment. Oncofertility counselling is recommended at the earliest opportunity and prior to cancer treatment, to help patients make informed decisions on pursuing fertility preservation. Currently, however, such discussions are not being routinely held.

In June 2017, an esteemed group of European oncofertility experts met to discuss current unfulfilled needs in oncofertility for female cancer patients. This expert group has produced here a number of key recommendations in order to guide oncologists, haematologists, and other involved professionals with oncofertility discussions and appropriate referrals for further fertility preservation counselling and follow-up.

1. Introduction

With increases in cancer incidence, infertility is a major concern for many women of reproductive age with newly diagnosed cancer (Angarita et al., 2016; Peddie et al., 2012; Donnez and Dolmans, 2017). Among female cancer survivors, overall pregnancy rates (adjusted for female age, education level and previous parity) are around 40% lower than in the general population (Peccatori et al., 2013).

Both chemotherapy and radiation therapy can be gonadotoxic (Stachs et al., 2017; Salama and Woodruff, 2017; Rodriguez-Wallberg and Oktay, 2014; Lambertini et al., 2017a; Wallace et al., 2003). Up to 80% of cancer survivors are affected by reduced fertility arising from their cancer treatment (Linkeviciute et al., 2014). Cytotoxic agents can accelerate the natural age-related decline in female follicular reserve, resulting in premature ovarian insufficiency (POI). It is estimated that the most commonly used combination chemotherapies typically advance a woman's reproductive age by around 10 years (Angarita et al., 2016; Roberts et al., 2015). Women receiving bone marrow transplantation (BMT) or high dose alkylating agents for leukaemia or Hodgkin's lymphoma are at a particular high risk of POI and the associated infertility (Schmidt et al., 2012).

Parenthood is important to most young cancer survivors. In a survey

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https://doi.org/10.1016/j.critrevonc.2019.03.010
Received 19 July 2018; Received in revised form 25 October 2018; Accepted 20 March 2019
1040-8428/

of young women undergoing cancer treatment, over half (51.7%) felt that having children was the "most important" issue in their life, with many wishing to use their own oocytes (Reh et al., 2011). In cases of patients with a very high desire to conceive their genetic offspring, the risk of treatment-related infertility may even affect their decision making about undergoing the suggested cancer treatment (Deshpande et al., 2015; Ruddy et al., 2014). It has also been reported that the issue of fertility becomes increasingly important for many women, even for those who initially said it was not that important to them (Thewes et al., 2003). Thus, the American Society of Clinical Oncology (ASCO) recommends the referral of cancer patients who are ambivalent or uncertain about their fertility intentions to a reproductive specialist for a fertility preservation consultation (Oktay et al., 2018).

Patient quality of life can be adversely affected by a threat or episode of treatment-related infertility, with patients experiencing emotional distress, fear, anxiety, and even moderate or severe depression (Angarita et al., 2016; Kort et al., 2014). Importantly, the thought of having children after a cancer diagnosis can be a powerful stimulus for recovery (Hershberger et al., 2013; Deshpande et al., 2015).

Despite the interest in parenthood expressed by many cancer patients, the number of patients who access fertility preservation remains relatively low (Goodman et al., 2012). Patients' lack of awareness of treatment-related infertility, together with the time pressures and conflicting priorities of physicians, are among the many factors which may hinder adequate oncologist-patient fertility discussions and timely referrals (Linkeviciute et al., 2014; Dolmans, 2018).

In addition, inter- and intra-country differences in oncofertility practice, set-up, and reimbursement exist (Table 1) (adapted from: ESHRE and Fertility Europe, 2017; Shenfield et al., 2017; HFEA, 2017). Although some public funding for assisted reproduction (ART) exists in almost all European Union (EU) member states, the extent of coverage and eligibility criteria differ. Despite this, ASCO recommends that "although disparities in access to this type of treatment are to be expected, no patients should be excluded from consideration for discussion" (Loren et al., 2013).

Our aim was to provide clinicians, and particularly oncologists, with a comprehensive reference when dealing with female cancer patients, focusing on young adults.

2. Materials and methods

Physicians and allied healthcare professionals with expertise in the field of assisted reproduction and oncology from several European countries were invited to participate in a 1-day expert consensus meeting on the topic of "cancer and fertility preservation in adult female cancer patients".

Experts provided an overview of the current status of fertility preservation for female cancer patients in their respective countries. They were also asked to identify specific clinical oncofertility practices that worked well in their individual clinics, in addition to any challenges faced.

On the basis of the data presented and subsequent multidisciplinary discussions, oncofertility recommendations were developed and are presented here. These recommendations should be used for guidance only. The specific needs of each patient should be individually assessed and treatment tailored accordingly.

The scopes of the present article are:

- To provide a practical set of recommendations to aid timely and adequate oncofertility discussions with adult female cancer patients.
- To aid oncologists and haematologists in their decision-making around referring female patients for fertility preservation and to support a multidisciplinary approach to oncofertility care and decisions.
- To provide information around currently available oncofertility resources.
- To provide examples of oncofertility best practice which may be appropriate for adoption locally.

Table 1
Oocyte and ovarian tissue cryopreservation regulations, indications, and funding in European countries when for medical reasons (2015 data).

Country	Specific regulation	Age limits (years)	Funded for medical purposes?
Austria	Law	No	No
Belgium	Law	< 45	Yes
Denmark	Law + guidelines	< 40	Yes
Finland	Law	No	Yes
France	Law + guidelines	18–42	Yes
Germany	Law + guidelines	< 43	No
Italy	Law + guidelines	No	Yes
Netherlands	Law + guidelines	No	Yes
Norway	Law	No	Yes
Portugal	Guidelines		Yes
Spain	Law + guidelines	> 18	Yes
Sweden	Law + guidelines	No	Yes
United Kingdom	Law + guidelines	No	No

Note: Legal right to medically-assisted reproduction varies between countries according to patient sexuality and marital status.

3. Results: The recommendations

3.1. Topic: Proactive and timely discussion of infertility risk with female cancer patients

The importance of adequate and timely physician-patient conversations around the risk of infertility in cancer patients is widely endorsed (Kim et al., 2016a; Oktay et al., 2018; Dolmans, 2018). Any healthcare professional involved with the cancer diagnosis should be prepared to have such conversations (Oktay et al., 2018). However, one recent study indicates that only 50% of doctors and nurses, and 24% of allied healthcare professionals, always address this issue with their cancer patients (Ussher et al., 2016).

A number of barriers to such oncofertility discussions exist on the part of physicians, institutions, and patients (Table 2) (Quinn et al., 2009; Peddie et al., 2012; Ussher et al., 2016; Shimizu et al., 2013; Louwé et al., 2018; Logan et al., 2018; Jones et al., 2017; Deshpande et al., 2015; Loren et al., 2013; Thewes et al., 2003; Benedict et al., 2015).

Every female cancer patient of reproductive age should be asked about their fertility intentions irrespective of the patient's parity, age or anticipated prognosis (Loren et al., 2013; Peccatori et al., 2013; Lambertini et al., 2016).

This discussion should be initiated by the oncologists, haematologists, or relevant involved professionals at or soon after the initial cancer diagnosis and before cancer treatment is initiated (Oktay et al., 2018). Such timely discussion assists the prompt referral of appropriate patients to fertility specialists. Use of an oncofertility consultation checklist could support the oncologist and haematologist in these discussions and referrals (example in Table 3). The discussion about the risk of infertility and the patient's fertility wishes, irrespective of outcome, should be documented in the medical records (Oktay et al., 2018). It is also preferable for the patient to sign a general Informed Consent Form which explains the side effects of cancer therapy and any associated risk of infertility, as was previously discussed between the oncologist and patient at the initial diagnosis and planning of treatment.

Recommendation 1: Proactive discussion of infertility risk should be undertaken with all relevant cancer patients at the earliest opportunity.

Table 2
Examples of physician, institutional and patient barriers in oncofertility discussions and referral.

Physician/institutional barriers, include:	Patient barriers, include:
• Limited available time for discussion of infertility risk/fertility preservation options • Concern about delaying cancer treatment for fertility preservation • Assumptions about the preservation procedure (complexity, time required etc.) • Assumptions regarding patient's own personal situation (affordability, existing children) • Difficulties in referring (i.e. lack of fertility contacts) • Concerns of a possible detrimental effect of a future pregnancy on prognosis especially for women with endocrine sensitive tumours	• Absence of knowledge regarding impact of chemotherapy or radiotherapy on fertility • Absence of knowledge on availability of fertility preservation methods • Feeling overwhelmed with their cancer diagnosis • Fear of having children after cancer due to a fear of a higher risk of malformations or risk of passing on a cancer diagnosis to a future child

Table 3
Example of oncofertility consultation checklist.

Item	Yes	No
At initial consultation		
• Patient asked about their fertility intentions?		
Patient eligibility for fertility preservation referral checked?		
• Age < 43 years?[a] (for oocyte freezing)		
• Age < 36 years? (for ovarian tissue freezing)		
• Has reasonable prognosis/general health status? Is to be treated with curative intent?		
• Gonadotoxicity of planned cancer treatment?		
• Suitability to undergo the fertility preservation procedure/surgery?		
• Is there time to undergo the fertility preservation procedure? Urgency of cancer treatment?		
• Previous fertility history? Number of children?		
Patient counselled?		
• About risk of premature ovarian insufficiency and/or infertility (high/medium/low/inexistent)		
• About the availability of fertility preservation techniques		
• Alternatives to fertility preservation exist (i.e. oocyte donation, gestational surrogacy, adoption)		
• Fertility preservation differs from ovarian function preservation		
• Menstruation is not indicative of fertility status		
Other considerations?		
• Involvement of the multidisciplinary team in decisions on patient care or care co-ordination (i.e. nurse navigator, mental health professionals)?		
• Patient referred for psychological assessment/support?		
• Existing collaboration with of an appropriate fertility centre for referral?		
Documentation?		
• Fertility intentions documented in patient's file?		
Following completion of cancer treatment		
• Patient referred back to fertility specialist after cancer treatment?		

[a] Criteria for age definition based on optimum chances of fertility success according to biological age. After 35 years, female fertility declines rapidly.

These are recommendations, however local laws and regulations should be followed, as should adaptation depending on clinical circumstances.

3.2. Topic: Providing information to allow the best decision regarding fertility preservation

3.2.1. Fertility risk

In order to make an informed choice, patients need to receive all appropriate information at an early stage regarding their specific infertility risk which varies with treatment type and dose, availability of fertility preservation techniques, pros and cons of fertility treatment, and likelihood of ART success (Jadoul et al., 2010). Female cancer patients say they are often dissatisfied with the fertility information received, mainly as a consequence of the topic not being addressed (Tschudin and Bitzer, 2009). They may experience long-term feelings of anger and injustice, if they feel that they were not offered adequate fertility counselling prior to starting cancer treatment (Canada and Schover, 2012). With already much for the patient to absorb, these women have suggested a need for the following (Deshpande et al., 2015):

- More written oncofertility information, given earlier in cancer treatment discussions and re-discussed over the course of treatment.
- Standardised, balanced oncofertility information.
- Information based on fertility preservation options rather than on infertility statistics.
- Access to experts, including counsellors, to help them in their decisions.

3.2.2. Fertility preservation options

Available female fertility preservation options usually fall into 5 main categories, each with differing eligibility criteria as previously described (Angarita et al., 2016; Kim et al., 2016a; Shapira et al., 2014; Harada and Osuga, 2016; Loren, 2015; Donnez and Dolmans, 2013). Each patient must be individually assessed since the patient's cancer diagnosis and personal situation will influence their suitability to undergo the different procedures. Fertility preservation procedures that can be offered will also depend on the regulations and ethical oversight in each country, and therefore general overarching guidance is not possible.

The most commonly used fertility preservation procedures are embryo and oocyte cryopreservation. They are considered the 'gold standard' techniques. These procedures require an available period of about 2 weeks prior to starting any cancer treatment for oocyte stimulation and retrieval to take place. Regarding ovarian tissue cryopreservation, although generally considered experimental, there have been over 130 live births to date and there are encouraging live birth rates (Donnez and Dolmans, 2017). Ovarian tissue cryopreservation is the only option for patients requiring immediate cancer treatment and for prepubertal patients.

In specific circumstances, ovarian transposition, fertility sparing surgery, or in vitro maturation of oocytes followed by oocyte or embryo vitrification may be options (Creux et al., 2018; De Vos et al., 2016; Segers et al., 2015). In addition, for patients who are candidates to receive chemotherapy, concurrent use of temporary ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) can be offered as an option but should not be considered as an alternative to cryopreservation strategies (Lambertini et al., 2017c). Current ASCO recommendations state that GnRHa may be offered to young women with breast cancer when proven fertility preservation methods are not feasible (Oktay et al., 2018). A recent meta-analysis of individual patient data from the largest randomised clinical trials in women with early breast cancer indicated the beneficial effects of GnRHa therapy in reducing POI risk and increasing post-chemotherapy pregnancy rates with no negative effect on patients' outcomes (Lambertini et al., 2018a). Another study did not show such beneficial effect in Hodgkin disease patients (Demeestere et al., 2016).

Oncologists and haematologists should counsel their patients during initial discussion on a number of key oncofertility issues, including:

- Anticipated gonadotoxic risk from their cancer treatment regimen (including risk of infertility and premature menopause).
- Impact of their cancer on appropriateness for fertility preservation, including cancer type, urgency of commencing cancer therapy, recurrence risk, disease prognosis (Loren et al., 2013; Kim et al., 2016a).

- A brief overview of the types of ART procedures available.
- Embryo and oocyte cryopreservation require the patient to be chemotherapy-naïve while ovarian tissue harvesting for cryopreservation may be undertaken after limited chemotherapy has commenced (although it is preferred prior to any systemic anticancer treatment).
- Preserving gametes, embryos, or preserving fertility does not guarantee having a pregnancy after treatment (Oktay and Turan, 2016; Diaz-Garcia et al., 2018).
- Referral to a fertility specialist or undergoing fertility preservation procedures does not necessarily delay the start of cancer treatment (Pavone et al., 2017; Letourneau et al., 2017; Chien et al., 2017).

Other useful information that the oncologist may wish to discuss:

- Cancer outcomes do not appear poorer in patients who have undergone fertility preservation procedures (Loren et al., 2013). This includes fertility preservation performed prior to neoadjuvant chemotherapy for breast cancer, although the data are limited on which to make strong conclusions (Chien et al., 2017; Kim et al., 2016b; Baynosa et al., 2009; Letourneau et al., 2017).
- Return of menstruation post-chemotherapy is not always indicative of a return to fertility. Data indicate that at least 40% of women aged 35 years who resumed normal menses following cancer treatment experienced infertility due to severely diminished ovarian reserve (Kort et al., 2014; Taylan and Oktay, 2017). Long-term ovarian function can be maintained by as little as 10% of the ovary, and so clinical measures of menstrual function are a poor indicator of ovarian damage (Wo and Viswanathan, 2009).

Fertility specialists should then provide further in-depth information on fertility preservation, including:

- Types of ART procedures, their pros and cons, and possible reimbursement status (Tables 1 and 4).
- Likely success rates of the different techniques (as below)and impact of patient age on potential success (Note: There is an absence of large controlled studies comparing the success rates of different techniques).
- Centre-specific fertility preservation success rates since these may vary from published rates (Donnez and Dolmans, 2017).
- Psycho-social and ethical issues raised by the process, where applicable.

Reported success rates from selected fertility preservation studies using different techniques show:

- Embryo cryopreservation and frozen-thawed embryo transfer in cancer patients: live birth rate (LBR) ranges from 20% to 45% (Dolmans et al., 2015; Oktay et al., 2015).
- Oocyte cryopreservation: LBR is 50% in women $\leq$35 years old and 22.9% in women > 36 years old (Cobo et al., 2016).
- Ovarian tissue cryopreservation and reimplantation: LBR ranges from 18.2 to 40% in the literature (Donnez et al., 2015; van der Ven et al., 2016; Diaz-Garcia et al., 2018; Meirow et al., 2016; Donnez and Dolmans, 2017; Jensen et al., 2017). The striking differences observed between centres are likely due to the small numbers of patients enrolled in each study, as well as differences in age at the time of cryopreservation.

Recommendation 2: Cancer patients should receive sufficient and timely oncofertility information in order that they may make an informed choice regarding fertility preservation options.

3.3. Topic: Involving the multidisciplinary team in oncofertility decisions

Although it is recognised that discussions about fertility among other critical and life altering topics are difficult, a formal oncofertility programme involving oncofertility care coordinators can ease the clinical burden on oncologists (Vu et al., 2017).

A multidisciplinary team (MDT) approach to fertility preservation decisions is advocated (American Society for Reproductive Medicine [ARSM] Practice Committee, 2013). An oncofertility team may include (amongst others) a medical oncologist and/or haematologist, gynaecologist, fertility specialist/reproductive endocrinologist, a nurse navigator, psychologist, psychosocial counsellor and a social worker (Loren et al., 2013).

Ideally, the patient should meet with physicians, nurses and mental health professionals over several visits to discuss their fertility preservation which allows for a more comprehensive evaluation to understand each individual patient's needs (ARSM Practice Committee, 2013). Patients may also need to seek advice around financial assistance.

Consider adopting a multidisclipinary (MDT) approach to oncofertility discussions and patient care. MDT meetings, either in person or via videoconference, are an opportunity to discuss fertility aspects of a cancer patient's care with all involved professionals. These allow for shared decisions around patient management. Allied healthcare professionals, such as nurses and psychologists, may offer much useful support to both the oncologist and patient.

Most guidelines recommend that patients should have access to psychological assessment and/or support (ASRM Practice Committee, 2013). In addition, studies have shown that including a nurse in the MDT results in the psychosocial needs of the patient being met more fully (Lamb et al., 2011; Srikanthan et al., 2016) A nurse navigator (and/or psychologist) can be instrumental to both improving the scheduling of oncofertility care to help avoid delays, as well as organising patient counselling.

Recommendation 3: A multidisciplinary approach to oncofertility decision-making and patient care should be considered.

The oncofertility patient navigator

> Fertility preservation services require easy access and swift and efficient procedure because of the limited time for urgent fertility preservation. An oncofertility patient navigator is a nurse or midwife specialised in reproductive medicine and oncology. He or she acts as a single person of contact who coordinates the clinical pathway of the oncofertility patient, in order to minimise the time frame for fertility preservation. The navigator integrates all medical information and facilitates multidisciplinary communication, leading to a shared decision on the oncofertility treatment. In this setting: urgent appointments and interventions for the patients are scheduled without any delay. The most important task of the nurse navigator is providing individualised counselling and coaching to provide knowledge and emotional empowerment of the patient. Guided by expert medical advice the nurse navigator may have an important contribution to the quality of care in oncofertility. Srikanthan et al. (2016) demonstrated in a retrospective chart review and prospective survey that implementation of a dedicated programme with a nurse navigator is associated with a higher probability of fertility discussion and fertility preservation referrals for young breast cancer patients.

Table 4
Fertility preservation options for cancer patients.

Fertility procedure	Ideal patient characteristics	Potential benefits	Potential drawbacks
Embryo cryopreservation	• Postpubertal • Has male partner • Has time for ovarian stimulation prior to starting cancer treatment (2 weeks) [a]	• Established technique – standard of care, widely available • More able to predict likelihood of success • Can be started any time of the cycle – both in the follicular and luteal phase	• Requires time for ovarian stimulation to be undertaken before oocyte collection[a] • Oocyte retrieval must be completed before cancer treatment initiated • Limited number of embryos usually generated per cycle • Potentially costly financially • Limited data in cancer patients on live births with the use of previously cryopreserved embryos
Oocyte cryopreservation	• Postpubertal women without a male partner, or women, who do not wish to fertilise their oocytes at the time of cancer diagnosis	• Established technique • Where ethical or religious objections to embryo cryopreservation exist • For women in countries where embryo cryopreservation is prohibited • Can be started any time of the cycle – both in the follicular and luteal phase	• Requires time for ovarian stimulation prior to cancer treatment[a] • Potentially financially costly • Limited data in cancer patients on live births with the use of previously cryopreserved oocytes
Ovarian tissue cryopreservation	• Prepubertal girls • Women who do not have sufficient time for ovarian stimulation prior to commencing cancer treatment • Women who wish to cryopreserve ovarian tissue	• Ovarian tissue harvesting requires 2–3 days • Minimal delay in initiating cancer therapy • Male partner and ovarian stimulation not required at the time of cancer diagnosis • Spontaneous conception can follow after transplantation • Can be performed at any time during menstrual cycle • Preserves a large number of primordial follicles • Low complication rate • Endocrine function may be restored following reimplantation of ovarian tissue • Experimental option for leukaemia patients in complete remission after chemotherapy	• Requires surgical procedure to harvest and reimplant tissue • Less suitable for patients with reduced ovarian reserve • Contraindicated in ovarian carcinoma or in cancers that metastasise to the ovaries • Ovarian tissue could potentially be seeded with malignant cells (high risk in leukaemia patients) • Less well established/used technique requires specialist centre
Ovarian transposition	• Women with planned pelvic radiation therapy	• Option for patient requiring local pelvic radiation • Ovarian tissue can be harvested in the same session	• Requires surgical procedure
Fertility-sparing surgery	• Women with certain early-stage gynaecological malignancies	• Ovaries and/or uterus are preserved	
In vitro matura-tion of oocytes	• Only used in special circumstances • (PCOS patients to avoid hyperstimulation)	• Minimal or no prior ovarian stimulation required • Can be completed in 2 – 6 days without any risk of OHSS • Immature oocytes can be collected in both the follicular and luteal phases	• Lower success rates than traditional IVF/ICSI • Very limited data in cancer patients on live births with the use of previously cryopreserved in vitro matured oocytes
GnRHa during chemotherapy	• Premenopausal breast cancer patients candidates to chemotherapy (any age)	• Only strategy studied within randomised controlled trials • Minimal delay in initiating cancer therapy • Wide availability • No surgical procedures needed • Can be performed at any time during menstrual cycle • Preserves ovarian function during treatment	• Limited data on success rates in terms of post-treatment pregnancies • Mechanism of action debated and poorly understood • Limited and conflicting evidence in women with tumours other than breast cancer

[a] May use shorter or random-start ovarian stimulation protocols which can be started during the follicular or luteal menstrual phases so reducing the time prior to starting cancer therapy.

AMH: anti-müllerian hormone; OHSS: ovarian hyperstimulation syndrome; IVF: in vitro fertilisation; ICSI: intracytoplasmic sperm injection; GnRHa: gonadotropin-releasing hormone agonist.

3.4. Topic: Establishing processes and networks to assist with fertility preservation referrals

A concern of both physicians and patients is that undergoing fertility preservation may delay the start of cancer treatment and potentially affect patient prognosis. However, studies do not indicate either significant delays to cancer treatment or poorer outcomes in these patients (Pavone et al., 2017; Letourneau et al., 2017; Chien et al., 2017). However, prompt referral to a fertility specialist is important to reduce the lag time between cancer diagnosis and the start of treatment (Baynosa et al., 2009; Lee et al., 2010).

Close collaboration between medical oncologists, haematologists, surgeons, and reproductive specialists is considered key (Baynosa et al., 2009; Ruddy et al., 2014; Cohen et al., 2016; Villarreal-Garza et al., 2017; Lambertini et al., 2017b). To facilitate efficient fertility preservation referrals, it is recommended that the oncologist or

haematologist proactively identifies local fertility referral centres and establishes relationships with local fertility specialists:

- Having a map (and a phone numbers list) of such fertility referral centres available may be useful.
- Appropriate fertility referral centres need to be able to offer a fertility specialist consultation within 24–48 h of referral where cases are urgent.

Physicians are also recommended to proactively identify any other possible sources of support potentially useful in supporting fertility preservation referrals i.e. oncofertility guidelines, local clinical networks, oncofertility programmes, standardised information for patients (see Supplemental Table 1).

3.5. Topic: Post cancer therapy: fertility follow-up

It is recommended that not only should fertility preservation be discussed as early as possible once a cancer diagnosis is made and before treatment commences, but it should also be discussed at follow-up post treatment or if pregnancy is being considered (Oktay et al., 2018).

In addition to prompt initial fertility referrals, it is recommended that patients are adequately followed up by the fertility specialist following the completion of cancer treatment. This optimises the chances of pregnancy occurring in these patients.

ESMO guidance states that there is no particular time when it is considered optimal to allow patients to become pregnant following their cancer diagnosis. Timings should consider factors such as time to completion of cancer treatment, risk of relapse, age, and ovarian function (Peccatori et al., 2013), in addition to patients wishes. Patients may have a number of questions relating to the pros and cons of pregnancy following a cancer diagnosis. Physicians need to be able to respond to these, so that such issues do not become barriers to patients seeking referral. Five key oncofertility-related clinical questions are reported together with the experts' responses in Supplemental Table 2.

Patients who initially expressed an interest in fertility preservation or were ambivalent, irrespective of their initial receipt of treatment, should be referred back to the fertility specialist after their cancer treatment has been completed or if pregnancy is being considered (Oktay et al., 2018). The timing of this should be personalised according to patient age, ovarian reserve, previous treatments, time of treatment completion, and individual risk of relapse (Peccatori et al., 2013) and patient wish. Referral is generally indicated when the patient is considered at lower risk of cancer relapse. This referral is also important to check the patient's general health status and need for hormone replacement therapy.

Regarding fertility issues post treatment, patients should be advised that:

- Ovarian reserve assessment should be undertaken at the earliest 12 months post-chemotherapy.
- A minimum 6–12 month lag time interval from the last cancer treatment to controlled ovarian stimulation (COS) or cryopreservation is generally expected. This time interval, however, is decided by the oncologist who gives the green light to the patient to try to conceive. For patients with endocrine sensitive tumours, limited data are available on the safety of performing ART procedures, and particularly COS, when they are not followed by anticancer systemic therapy (Goldrat et al., 2015). However, considering that having a pregnancy appears to be safe also in patients with hormone receptor-positive disease (Lambertini et al., 2018b), it is reasonable to assume the lack of negative prognostic effect of this approach.

Recommendation 5 (:). Cancer patients expressing an initial interest in fertility preservation should be referred back to the fertility specialist following completion of their cancer treatment.

4. Conclusion

Following improvements in the prognosis of cancer patients, advances in fertility preservation techniques, and an increased confidence of the safety of pregnancy after cancer treatment, the possibility of having a family after treatment is becoming a reality for female cancer survivors. To help achieve the best outcomes for these patients, a number of key recommendations have been presented to help ensure all patients are made aware of, and can access, fertility preservation treatment.

Oncologists and haematologists are very important players in oncofertility practice as, seeing cancer patients at the time of diagnosis, they are the best placed to initiate early conversations around infertility risk and help identify appropriate patients for fertility preservation. They, working alongside the multidisciplinary team, are responsible for the referral process to the fertility specialist and to others in the oncofertility team, such as nurses and psychologists. This early intervention ensures that patients are less likely to miss out on receiving time-critical fertility information which is potentially crucial to their chances of having children.

Proactively establishing a strong network with local fertility clinics and fertility experts is recommended to ease the referral process, as is the availability of oncofertility resources to provide to the patient help with their decision-making at this very emotional time.

Following completion of cancer treatment, referral of any interested patients back to a fertility counsellor or fertility specialist will help address any outstanding patient needs around pregnancy.

Take-home messages:

1. Oncologists, haematologists and allied professionals should address the issue of cancer-related infertility with all female patients of reproductive age at the earliest opportunity (ideally at cancer diagnosis and prior to treatment).
2. Patients interested in future childbearing, or even those that are ambivalent or uncertain, should be referred to a reproductive specialist to be given relevant information on fertility preservation options in order to make an informed decision.
3. To enhance speed of referrals and ease clinical burden, it is recommended that physicians have an up-to-date map and phone numbers list of local fertility clinics to whom patients can be referred and that standardised oncofertility resources are available to be given to patients.
4. A multidisciplinary team approach to oncofertility decisions and patient care is recommended; involving a navigator nurse to facilitate the organisation.
5. Patients may have a number of questions relating to the pros and cons of pregnancy following a cancer diagnosis. Physicians need to be able to respond to these, so that such issues do not become barriers to patients seeking referral.
6. Patients should be referred to the gynaecological endocrinologist after completion of cancer therapy for assessment of need for hormone replacement until ovarian function recovers, as well as for potential fertility assessment.

Declaration of interest

MMD, ML KL, TAS, ARS, AB, VB, FL, EVM, AG, have no conflict of interest.

Acknowledgements

This work was funded by Teva Pharmaceuticals Europe, Women's Health Division (now Theramex HQ UK Limited).

The authors thank Rachel Hutchings, PhD, BPharm (Hons) for medical writing and editorial assistance, which was funded by Teva/Theramex.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.critrevonc.2019.03.010.

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