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Gender-specific aspects related to type of fertility preservation strategies and access to fertility care

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ABSTRACT

Survivorship is an area of paramount importance to be addressed as early as possible after cancer diagnosis by all health care providers. On this regard, cancer care in young patients often poses several age-related considerations among which fertility and pregnancy-related issues have a crucial role. According to the available guidelines on the topic, all patients with cancer diagnosed during their reproductive years should be provided a proper oncofertility counselling before starting anticancer treatments. This is an important step in order to inform patients about the potential treatment-induced gonadotoxicity and the available strategies for fertility preservation so that they can be referred as early as possible to fertility specialists if potentially interested in these options.

In this manuscript, we aim to provide an up to date overview on the available efficacy and safety data with the main strategies for fertility preservation in male and female cancer patients in order to help optimising the oncofertility counselling performed by healthcare providers involved in cancer care and dealing with young patients. In male patients with cancer, sperm cryopreservation is the standard technique for fertility preservation. Oocyte/embryo cryopreservation, ovarian tissue cryopreservation and temporary ovarian suppression with luteinising hormone-releasing hormone agonists during chemotherapy are the main options in female patients with cancer.

A multidisciplinary management building a strong network between fertility and oncology/haematology units is crucial to properly address fertility care in all young patients with cancer, at both diagnosis and during oncologic follow-up. Discussing fertility and pregnancy-related issues with young patients with cancer has to be considered mandatory nowadays keeping in mind that returning to a normal life (including the possibility to have a family and to live with as few side effects as possible) should be considered an important ambition in cancer care in the 21st century .

INTRODUCTION

In 2012, approximately one million new cancer cases have been diagnosed in young adults between the ages of 20 and 39 years.[1] Global cancer burden in these patients varies substantially by sex, age, development level and geographical region; liver and testicular cancers are the two most commonly diagnosed malignancies among young male patients while breast and cervical cancer are the most frequent diagnosis in young female patients.[1] Nowadays, thanks to improved survival rates, many cancer survivors face the consequences of short-term and long-term treatment-induced side effects; hence, survivorship is an area of paramount importance to be addressed as early as possible after cancer diagnosis by all healthcare providers.[2]

Cancer care in young patients often poses several age-related considerations among which fertility and pregnancy-related issues are of major importance. Anticancer therapies may have potential detrimental effects on the gonadal function and fertility potential of young patients.[3–7] Treatment-induced gonadotoxicity is of concern to many young patients with newly diagnosed cancer.[8–12] According to the available guidelines on the topic, all patients with cancer diagnosed during their reproductive years should be provided a proper oncofertility counselling before starting anticancer treatments.[13 14] Nevertheless, the knowledge and attitudes of healthcare providers towards this important issue remain suboptimal.[15–17]

In the last years, the available evidence on fertility preservation in patients with cancer has markedly increased. In this manuscript, we aim to provide an up to date overview on fertility preservation in male and female cancer patients in order to help optimising the oncofertility counselling performed by healthcare providers involved in cancer care and dealing with young patients. The available efficacy and safety data with the main strategies for fertility preservation in male (sperm cryopreservation) and female (oocyte/embryo cryopreservation, ovarian tissue cryopreservation and temporary ovarian suppression with luteinising hormone-releasing

Table 1 Characteristics of the main available strategies for fertility preservation in male and female patients with cancer

	Type of strategy	Definition	Experimental or standard	Access to fertility unit needed	Hormonal stimulation needed	Potential delay in anticancer therapy initiation	Surgery needed	Fertility preservation outcomes	Gonadal preservation outcomes
Male patients	Sperm cryopreservation	Freezing a sample of sperm to be used for IUI/IVF/ICSI	Standard	Yes	No	No	No	Clinical pregnancy rate per cycle: ▶ 13%–14.3% using IUI ▶ 24.1%–30% using IVF ▶ 30.1%–50.3% using ICSI	NA
Female patients	Embryo cryopreservation	Harvesting eggs, IVF, and freezing of embryos	Standard	Yes	Yes	Yes	Yes	Live birth rate: ▶ 13.2% per embryo (25–29 years) ▶ 9.8% per embryo (35–39 years)	NA
	Oocyte cryopreservation	Harvesting and freezing of unfertilised eggs	Standard	Yes	Yes	Yes	Yes	Live birth rate: ▶ 8.7% per oocyte (<30 years) ▶ 1.1% per oocyte (43–44 years)	NA
	Ovarian tissue cryopreservation	Freezing of ovarian tissue and reimplantation after cancer treatment	Experimental/ standard	Yes	No	No	Yes	Live birth rate approximately 40% (≤36 years)	Ovarian function restoration in 90% of patients in 4–9 months
	Ovarian suppression with LHRHa	Use of hormonal therapies to protect ovarian tissue during chemotherapy	Standard*	No	No	No	No	Pregnancies: ▶ 30 vs 20 without LHRHa IRR 1.83 95% CI 1.06 to 3.15 (breast cancer) ▶ 17 vs 18 without LHRHa RR 1.13 95% CI 0.66 to 1.93 (lymphoma)	POI rates: ▶ 14.1% vs 30.9% without LHRHa OR 0.38 95% CI 0.26 to 0.57 (breast cancer) ▶ 18.9% vs 32.1% without LHRHa RR 0.70 95% CI 0.20 to 2.47 (lymphoma) 33.3% vs 0.0% without LHRHa (ovarian cancer)

*For ovarian function preservation, mostly in patients with breast cancer.
ICSI, intracytoplasmic sperm injection; IRR, incidence rate ratio; IUI, intrauterine insemination; IVF, in vitro fertilisation; LHRHa, luteinising hormone-releasing hormone agonist; NA, not applicable; POI, premature ovarian insufficiency; RR, relative risk.;

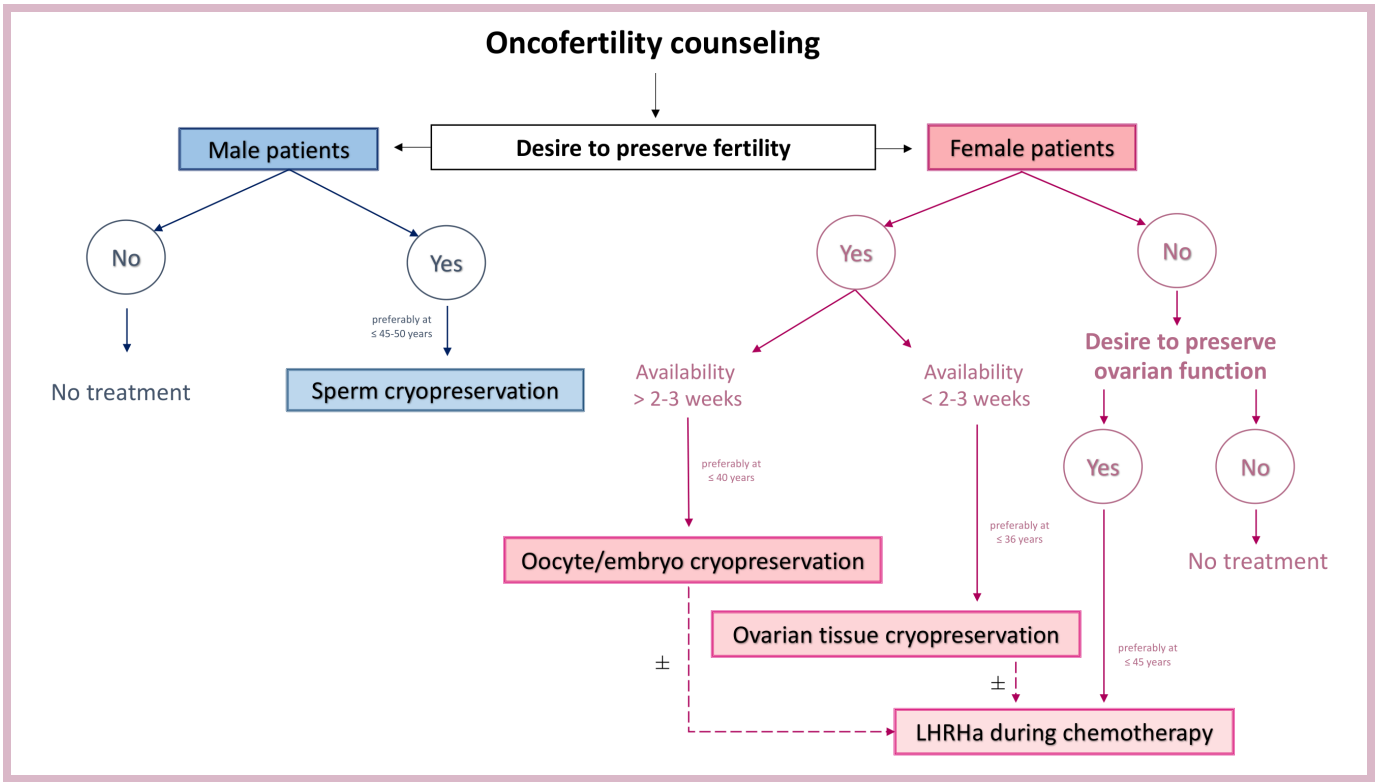

Figure 1 Proposed algorithm for managing fertility preservation in male and female patients with cancer[i]. LHRHa, luteinising hormone-releasing hormone agonist.

[i]Adapted from the recently published ESMO (European Society for Medical Oncology) guidelines on fertility preservation in patients with cancer.[13]

hormone agonists (LHRHa)) patients with cancer are reviewed.

CONCEIVING AFTER CANCER

The majority of young patients with cancer report a strong interest in having biological children.[18] However, despite the increasing availability of fertility preservation techniques, cancer survivors have reduced chances of conceiving following completion of anticancer treatments as compared with the general healthy population of a similar age,[19 20] with higher rates for male (hazard ratio [HR] 0.74, 95% confidence intervals [CI] 0.71 to 0.78) than female (HR 0.61, 95% CI 0.58 to 0.64) patients.[19] Nevertheless, the rates of post-treatment pregnancies appears to be similar to those of the general population for male and female survivors of melanoma and thyroid cancer.[19 20] Among women, the chances of post-treatment pregnancies are particularly low for breast cancer survivors with prior history of hormone receptor-positive disease.[21 22]

Young cancer survivors and their treating oncologists/haematologists may express different concerns when considering to conceive following completion of anticancer treatments.[16 23] However, evidence has become available to dispel most of them.

Globally, many studies have shown no apparent increased risk of congenital abnormalities for pregnancies of male and female cancer survivors with prior exposure to anticancer treatments.[24–28] However, some studies have reported potential increased risks. Specifically, a slightly higher risk of congenital abnormalities was described in men using cryopreserved sperm or fresh post-treatment sperm; however, no strong conclusions can be derived on this regard considering the limited evidence coming mostly from register-based studies.[29] Similarly, a recent metanalysis has shown a slightly higher risk of congenital abnormalities in babies born from women with prior cancer history; however, this result was considered being likely an artefact of the analysis.[30]

In terms of risk of developing pregnancy complications (including abortion, caesarean delivery, postpartum haemorrhage, preterm birth, small for gestational age, low birth weight), a higher risk for post-treatment pregnancies of adult women with prior cancer history has been described,[25 26 30–35] while this has not been shown for male patients and their healthy partners.[25] Notably, off-target effects of chemotherapy and radiotherapy in

female patients may also be associated with structural and/or vascular uterine damages that can potentially lead to pregnancy complications.[36] Therefore, post-treatment pregnancies in female cancer survivors should be monitored more closely than those in healthy women.

Safety concerns on the potential detrimental prognostic effect of pregnancy have been expressed for patients with hormone sensitive cancers.[16] Recent data have dispelled these concerns.[28 37–40] A meta-analysis of 19 retrospective (10 case–control and 9 cohort) studies showed that women with a pregnancy after prior history of breast cancer had a non-significant reduced risk of recurrence (HR 0.84, 95% CI 0.69 to 1.02) and a significantly improved overall survival (HR 0.63, 95% CI 0.51 to 0.79) as compared with those without a subsequent pregnancy.[37] When including only the studies that controlled for the 'healthy mother effect' similar results were obtained with a reduced risk of death for women who had a subsequent pregnancy (HR 0.65, 95% CI 0.52 to 0.81).[37] More recent findings from a large population-based retrospective cohort study,[38] and a retrospective analysis within a phase III randomised trial,[28] confirmed the lack of detrimental prognostic effect for post-treatment pregnancies in young breast cancer survivors. One large retrospective case–control study had specifically addressed the safety of conceiving in women with prior history of hormone receptor-positive breast cancer.[39 41] Updated results after a median follow-up of approximately 10 years from initial breast cancer diagnosis showed no difference in disease-free survival (HR 0.94, 95% CI 0.70 to 1.26) nor in overall survival (HR 0.84; 95% CI, 0.60 to 1.18) between patients with or without a subsequent pregnancy after prior history of oestrogen receptor-positive disease.[39] Among women with oestrogen receptor-negative breast cancer, those with a post-treatment pregnancy had similar disease-free survival (HR 0.75; 95% CI 0.53 to 1.06) but better overall survival (HR 0.57; 95% CI 0.36 to 0.90) than patients without a subsequent pregnancy. No impact on patients' outcomes was shown for abortion, time to pregnancy and breastfeeding.[39] Recent data have also supported the safety of pregnancy after breast cancer in young patients carrying germline *BRCA* pathogenic variants.[40] This is highly relevant new information that can be shared during the oncofertility counselling of these patients considering the limited evidence available on this regard,[42 43] and physicians' safety concerns.[44]

Although there is no contraindication to pregnancy after treatment completion in breast cancer survivors irrespective of their tumour subtype,[45] there is no proper evidence to counsel women with history of hormone receptor-positive breast cancer who are receiving 5–10 years of adjuvant endocrine therapy on the safety of a temporary treatment interruption for trying to conceive. An international multicentre trial (POSITIVE study: NCT02308085) investigating this issue has recently completed accrual and is expected to provide an important answer on this regard.[46]

FERTILITY PRESERVATION IN MALE PATIENTS WITH CANCER

Sperm cryopreservation

Sperm cryopreservation is the standard strategy for fertility preservation in male cancer patients (preferably aged ≤45–50 years) about to undergo gonadotoxic therapies or cancer surgery at risk of infertility and who may desire children in the future.[47] It is a widely available method but a multicollaborative care pathway should be implemented in order to provide the patients with rapid and easy access to reproductive specialists and lab facilities for sperm cryopreservation.[48] The most effective and widely adopted fertilisation method is represented by intracytoplasmic sperm injection (ICSI).[49]

In patients undergoing sperm cryopreservation, semen can be collected by masturbation, which is the most used whenever feasible, or by assisted ejaculation techniques such as penile vibratory stimulation, electroejaculation or testicular biopsy, when the patient cannot ejaculate by masturbation.[50]

The actual usage rate of sperm cryopreserved before starting anticancer therapies accounts for approximately 10%.[51] In terms of efficacy, although large series are scarce, the rates of success using cryopreserved sperm from cancer patients for assisted reproduction are similar to or higher than outcomes with standard procedures used to treat infertile couples. A large study examined the rate of success of semen cryopreservation in 118 patients affected by different tumours: a total of 169 in vitro fertilisation (IVF)—ICSI were performed with a clinical pregnancy rate of 56.8%.[52] Consistently with the literature, a significant higher pregnancy rate was registered using ICSI (50.3%, 85/169 effective cycles) compared with IVF (24.1%, 13/54 effective cycles).[52] More recently, a systematic review included 30 studies and a total of 11 798 male patients with cancer who underwent sperm cryopreservation.[53] The rate of success of assisted reproductive techniques (ART) was 23% in terms of clinical pregnancy per cycle (95% CI 21% to 26%) irrespectively of the fertilisation method used. When considering IVF comparing to intrauterine insemination (IUI), significantly better outcomes were observed: the clinical pregnancy rate per cycle was 30% (95% CI 27% to 34%) for IVF and 13% (95% CI 10% to 17%) for IUI. As expected, IVF provides higher chances of pregnancy per cycle instead of IUI of thawed semen.[53] The three main techniques (IUI, IVF and ICSI) were compared by van Casteren *et al* in a cohort of cancer patients with cancer.[54] A total of 629 men who cryopreserved their semen were analysed. Out of the 37 couples who used the cryopreserved samples, 7 cycles of IUI, 32 of IVF and 53 of ICSI cycles were performed. The clinical pregnancy rate per cycle reported was 14.3% for IUI, 25% for IVF and 30.1% for ICSI.[54]

Notably, the ICSI procedure is the technique that revolutionised the effectiveness of sperm cryopreservation, allowing fertilisation even when the quality of the semen is poor (oligoasthenozoospermia, low mobility). For this

reason, this approach should be considered the preferred method when available.[54]

As previously highlighted, despite the controversial and limited available literature on this regard, patients should be informed about a slightly increased risk of congenital abnormalities in offspring of cancer survivors obtained with cryopreserved sperm or fresh post-treatment sperm.[29]

FERTILITY PRESERVATION IN FEMALE PATIENTS WITH CANCER

Oocyte/embryo cryopreservation

Oocyte/embryo cryopreservation before starting anticancer therapies is a standard strategy and the first option to be proposed to all female cancer patients (preferably aged ≤40 years) who wish to preserve their fertility.[13 14] This strategy requires approximately 2 weeks of controlled ovarian stimulation before oocyte pick up; this amount of time is mandatory for the procedure. Despite the possibility to initiate controlled ovarian stimulation also during the luteal phase with the so-called 'random-start stimulation' protocols,[55–58] this strategy cannot be proposed to patients who have urgent need to start anticancer treatment. On the contrary, in women who can delay the start of anticancer therapies of more than 4 weeks, a double controlled ovarian stimulation, beginning after picking up the former oocytes stimulated, can be considered to increase the potential chances of success.[59]

Although the success in cryopreserving oocytes has improved also thanks to the development of vitrification,[60] more limited efficacy data than with embryo cryopreservation are available in patients with cancer.[61] The limits of cryopreserving unfertilised oocytes might be referred to their biological characteristics: they are retrieved in metaphase II of cellular cycle and are large cells with a low ratio between surface and volume, highly capable of retaining water and thus to be potentially damaged during the freezing procedure.[61] They also are particularly vulnerable to osmotic stress caused by cryoprotective agents applied in order to preserve the cell from the intracellular ice-formation during the process. Cryopreservation has shown to also impact the genomic material in the nucleus of the oocyte, by deregulating genes involved in protection from oxidative stress, cell cycle and structural cell maintenance.[62] Nevertheless, oocyte cryopreservation is largely used and preferred also considering that it provides a patient reproductive autonomy. This technique is suitable to women who do not have a partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing as well as in countries like Italy where embryo cryopreservation in cancer patients is not allowed by law. Notably, it was demonstrated that storage time does not affect the transcriptome of cryopreserved mature oocytes,[63] which is particularly relevant for cancer survivors that may use their material several after years after cryostorage. Despite the limited data on the efficacy of oocyte cryopreservation specifically in the oncological population, the response to controlled ovarian stimulation could be considered the same as the non-cancer population.[64]

The success of oocyte/embryo cryopreservation is strongly dependent on the number of mature oocytes collected following controlled ovarian stimulation which is strongly influenced by the age and ovarian reserve of the patient at the time of the procedure.[65] The live birth rates using all cryopreserved oocytes after one stimulation cycle are around 35% in women <35 years.[66 67] In women around 40 years of age, the success rates are substantially lower.[66 68] Specifically, a study showed that the age-associated live birth rate per warmed oocyte ranged from 8.7% in women aged <30 years to 1.1% in women aged 43–44 years, with an overall oocyte to child efficiency of 6.7%.[69] Recent data indicate that oocytes from women with cancer show reduced fertilisation rates and embryos lower implantation rates than in women freezing oocytes for non-medical reasons, resulting in a lower live birth rate.[68] In women under 36 years of age, oocyte survival was 81.2% vs 91.4%, implantation rates 32.5% vs 42.6%, and cumulative live birth rates 41.1% vs 68.8% in patients with or without cancer diagnosis, respectively.[68] A reduction in the number of retrieved oocytes in cancer patients has not been shown by other studies.[65] Even when analysing the efficacy profile of embryo cryopreservation, live birth rate is strongly related to the age of the patients at the time of the procedure: the chances of pregnancy per embryo implanted ranged from 13.2% at the age of 25–29 years to 9.8% at the age of 35–39 years.[66]

In terms of safety, controlled ovarian stimulation can lead in rare cases to high-grade hyperstimulation[70]; pelvic infection and ovarian bleeding are potential but uncommon complications during the pick-up. The main safety concern with controlled ovarian stimulation is its use in patients with breast cancer particularly in those with estrogen-sensitive tumours.[16] The limited evidence on this regard suggests the lack of potential detrimental effect of the ovarian stimulation on breast cancer outcomes.[71–73] However, more prospective efforts are needed on this regard.[74 75] For trying to counteract the possible negative effect of the increased oestrogen serum concentration during controlled ovarian stimulation, alternative protocols including the use of letrozole[76 77] or tamoxifen[78] have been developed. Considering the larger and prospective available data with the use of letrozole, this agent should be preferred to be added to controlled ovarian stimulation protocols in breast cancer patients.[79]

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation is an alternative strategy to preserve fertility before starting gonadotoxic treatments.[13 14] The experimental designation has been recently revised,[80 81] and some countries already consider it to be a standard strategy,[82] which can be offered preferably to women aged ≤36 years. Importantly, this is the only option available for prepubertal girls.[83]

The main advantages over oocyte/embryo cryopreservation are represented by the short timeframe to perform

the procedure (controlled ovarian stimulation is not required), and the possibility to preserve not only fertility but also gonadal function. For this reason, the best candidates to ovarian tissue cryopreservation are patients who do not have enough time before starting anticancer therapies to perform ovarian stimulation for oocyte/embryo cryopreservation. However, it should be highlighted that this is a more complex surgical procedure consisting in biopsies of the ovarian cortex or unilateral ovariectomy usually done by laparoscopy, and then subsequent transplantation following the end of anticancer treatments. To cryopreserve ovarian cortex, despite encouraging results have been reported with vitrification, slow freezing is still the standard method.[84] Although this technique should be performed only in centres with the adequate expertise, ovarian surgery can be done locally and tissue transported to a central laboratory (with the so called 'hub and spoke' model).[85]

Ovarian function restoration has been reported in more than 90% of transplanted patients within 4–9 months, and the duration of ovarian functions ranges from less than 1 up to 10 years (mean 4–5 years).[85 86] To date, almost 200 babies have been born with the use of this procedure, with a live birth rate per patient estimated to be approximately 40%.[87] Age (together with the expertise of the centre) is the strongest determinant for the success of this strategy: ovarian tissue cryopreservation should not be proposed to patients older than 36 years.[88] Half of the pregnancies reported so far were natural conceptions, while around one third where conceived by ART.[87] Notably, there is not uniformity on whether ART treatment should be initiated right after transplantation or women should be allowed a period to attempt natural conception before.[89] On one hand, since ovarian function is restored in the majority of patients, a natural and less invasive approach could be preferred by women.[90 91] However, other groups claim that immediate ART treatment after regaining ovarian function maximises the chances of success, because of a greater pool of follicles available.[82]

In terms of safety, while surgical complications with ovarian tissue cryopreservation are rare, the main concern with its use in oncology is represented by the potential risk of reintroducing cancer cells at the time of transplantation (eg, for patients with leukaemia).[92] Hence, special attention should be paid in analysing the tissue before any transplantation procedure. The possibility to perform ovarian tissue cryopreservation after a first course of gonadotoxic treatment in order to decrease the risk of transplanting cancer cells has been successfully reported in a patient with leukaemia.[93] The possibility to grow follicles from ovarian tissue fragments in vitro, in a matrix of fibrin ('the artificial ovary'), is being studied, but without clinical application in humans yet.[94] However, since patients will probably use the cryopreserved tissue many years after the diagnosis, the state of art may change.

Another important concern is represented by the use of this strategy in patients with hereditary cancer syndromes associated with an increased risk of ovarian cancer like in women with germline *BRCA* pathogenic variants.[43] Despite the success of the strategy has been reported also in *BRCA*-mutated patients,[95 96] this is not the preferred option in this setting.

LHRHa during chemotherapy

Temporary ovarian suppression with the use of LHRHa during chemotherapy has been developed as an option to reduce the gonadotoxicity of cytotoxic systemic therapies in order to avoid endocrine-related side effects associated with the development of premature ovarian insufficiency (POI).[97] This option has not been studied as a fertility preservation strategy.[97] Therefore, it should not be considered an alternative to cryopreservation strategies and, on the other hand, it can be offered also to all premenopausal women (preferably aged ≤45 years) without pregnancy desire. Notably, the biological rationale behind its protective effect remains to be defined.[98–101] Nevertheless, after many years of debate on the efficacy and safety of this approach,[102–106] recent clinical data have led current guidelines to recommend its use as a strategy to preserve ovarian function during chemotherapy, mainly in the case of young women with breast cancer.[13 14 107–110]

Most of the evidence available on the efficacy and safety of this strategy exists for premenopausal patients with breast cancer. In this setting, most of the randomised trials have shown a statistically significant reduction in the risk of developing chemotherapy-induced POI with concurrent use of LHRHa.[98] The highest level of evidence derives from an individual patient-level meta-analysis that included 873 patients randomised in five breast cancer trials.[111] The rate of chemotherapy-induced POI was significantly reduced from 30.9% to 14.1% with the use of LHRHa (adjusted odds ratio [OR] 0.38, 95% CI 0.26 to 0.57). Moreover, a higher number of patients treated with LHRHa during chemotherapy had a post-treatment pregnancy (37 vs 20; incidence rate ratio 1.83, 95% CI 1.06 to 3.15) suggesting a potential fertility preservation role of this option. All patients irrespective of hormone receptor status, age, type and duration of chemotherapy derived benefit from the administration of LHRHa during chemotherapy.[111] Similar results were observed in a large metanalysis based on abstracted data from 12 randomised trials conducted in breast cancer patients.[112]

In premenopausal women with haematological malignancies, no protective effect of LHRHa use during chemotherapy was observed.[113–115] In a recent meta-analyses including 3 trials and 109 patients, similar POI rates (18.9% vs 32.1%; risk ratio [RR] 0.70, 95% CI 0.20 to 2.47) and post-treatment pregnancies (17 vs 18; RR 1.13, 95% CI 0.66 to 1.93) were observed between patients treated with LHRHa during chemotherapy or cytotoxic therapy alone.[116]

One randomised trial including 30 patients with ovarian cancer showed that LHRHa use during chemotherapy significantly reduced the rates of POI (33.3% vs 0.0%; p=0.02) but did not report post-treatment pregnancies.[117]

Regarding the safety of this strategy, administering LHRHa during chemotherapy increases the risk of developing menopausal symptoms (hot flashes and sweating); in most of the cases, they are of low severity and reversible.[111] Prior concerns for breast cancer patients with hormone receptor-positive disease on a potential detrimental antagonism between chemotherapy and an endocrine agent have been recently dispelled with the observation of similar survival outcomes between patients receiving systemic cytotoxic therapy with or without concurrent LHRHa.[111 118] In these patients, considering the known prognostic value of chemotherapy-induced amenorrhea and the role of ovarian function suppression,[119–121] prolonging treatment with LHRHa up to 5 years should be considered as part of adjuvant endocrine therapy.[109 110 122]

CONCLUSIONS

Having a family after prior cancer diagnosis and treatment completion is feasible but timing is crucial. A proper oncofertility counselling should be scheduled with all patients with cancer diagnosed during their reproductive years before treatment initiation.[13 14] This is a crucial step to inform patients on the potential gonadotoxicity of the proposed anticancer therapies and to offer them the available strategies for fertility preservation (table 1) (figure 1).

Implementing a strong network between fertility and oncology/haematology units is crucial to properly address fertility care in all young patients with cancer and for improving the access to fertility preservation strategies. A 'hub and spoke' model should be considered on this regard with different oncology/haematology units referring patients to centralised and more experienced fertility units.[123] Nowadays, the oncofertility unit has to be considered integral part of the management of cancer patients not only at diagnosis but also during oncologic follow-up after the completion of anticancer therapies.[12] In fact, it is important both to counsel patients on access to fertility preservation strategies before starting treatment in order to achieve future pregnancies and also to take care of their quality of life, sexuality, contraception and administration of specific therapies controlling the adverse effects of anticancer therapies.[12 124] In this perspective, the oncofertility counselling assumes a wider significance and should be conducted in parallel with oncological follow-up, even when the patient does not desire (or desire yet) a pregnancy.

Discussing fertility and pregnancy-related issues with young cancer patients has to be considered mandatory nowadays keeping in mind that returning to a normal life (including the possibility to have a family and to live with as few side effects as possible) should be considered an important ambition in cancer care in the 21st century.

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