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Beyond fertility preservation: role of the oncofertility unit in the reproductive and gynecological follow-up of young cancer patients

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STUDY QUESTION: Are there reasons that motivate young cancer survivors to ask for follow-up visits at an oncofertility unit?

SUMMARY ANSWER: Cancer survivors request oncofertility follow-up visits for the management of treatment-related side effects or ovarian reserve evaluation, even if not (or not yet) wishing for a pregnancy.

WHAT IS KNOWN ALREADY: Personalised oncofertility counselling before gonadotoxic therapies is considered standard of care for young women with newly diagnosed cancer. However, the long-term follow-up of these patients in an oncofertility unit is not described in the literature other than for the use of cryopreserved material.

STUDY DESIGN, SIZE, DURATION: We retrospectively examined rates and reasons for the first follow-up visits of 154 consecutive young female cancer patients (age range: 18–40 years) who underwent a pre-treatment consultation between January 2012 and June 2017. Demographic and clinical data were collected, as well as information about the chosen fertility preservation method, if any.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Rates and reasons for follow-up visits were collected and expressed as percentages. Different reasons were examined in the whole cohort and stratified for type of malignancy. Possible predictive factors for return to the follow-up visit (age, nulliparity, presence of a partner, neoplasm, having cryopreserved material) were investigated through logistic regression.

MAIN RESULTS AND THE ROLE OF CHANCE: Out of 154 patients, 74 returned to the oncofertility unit (48.1%) for a follow-up visit. The first visit was requested mostly at the end of anticancer therapies (51.3% versus 40.5% during therapies and 8.1% after cancer relapse). Among these patients, only 10.8% returned for the first time because they were actively desiring a pregnancy. For the others, the most common reasons for consultations were management of gynecological adverse effects of therapies (29.7%) and evaluation of ovarian reserve not linked to an immediate desire for a pregnancy (39.2%). Other patients asked for contraception (4.1%), menopause counselling (5.4%), or new fertility preservation counselling because of cancer relapse (10.8%). None of the examined factors were significantly predictive of return to the oncofertility unit.

LIMITATIONS, REASONS FOR CAUTION: These findings represent the experience of a single centre. A longer duration of follow-up would be needed to provide more precise information on this regard.

WIDER IMPLICATION OF THE FINDINGS: The role of an oncofertility unit should not be limited to proposing fertility preservation procedures. In the management of young adult cancer patients, the reproductive medical specialist should be considered a key figure not only before but also during and after anticancer treatments to explore salient aspects of gynecological and reproductive health.

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Introduction

Cancer diagnosis in women of reproductive age accounts for 3–10% of cancer worldwide (Fidler *et al.*, 2017; Siegel *et al.*, 2019). While life expectations for these patients have significantly increased in the past decades, a high proportion of them require therapies that are potentially gonadotoxic (Lambertini *et al.*, 2016). Cryopreservation techniques developed for infertility treatments have been applied for fertility preservation since the late 1990s and ultimately has led to an increased role of oncofertility units in the management of these patients (Diaz-Gacia *et al.*, 2018; Cobo *et al.*, 2018; Gellert *et al.*, 2018; Massarotti *et al.*, 2017). Several scientific societies have developed specific guidelines focused on fertility preservation to underline the importance of oncofertility counselling in young women who are candidates to potentially gonadotoxic treatments due to a newly diagnosed cancer (Oktay *et al.*, 2018; Peccatori *et al.*, 2013; International Society for Fertility Preservation, 2012; Ethics Committee of American Society for Reproductive Medicine, 2013; ASRM, 2013b; Lambertini *et al.*, 2017a).

While the role of reproductive medical specialists for the management of young cancer patients is well-established at the time of diagnosis, the need for this professional figure during oncological follow-up is less clear for survivors, except for those willing to undergo assisted reproductive technology procedures using their cryopreserved material. The utilisation rate for frozen embryos is reported to be 10–23% in small cohorts of cancer patients (Barcroft *et al.*, 2013; Dolmans *et al.*, 2015; Luke *et al.*, 2016), and data about frozen oocytes and ovarian tissue utilisation rates, although still incomplete and inconclusive, are around 5% (Diaz-Garcia *et al.*, 2018; Martinez *et al.*, 2014; Drukenmiller *et al.*, 2016). No other reasons for a follow-up at the oncofertility unit are reported and its potential long-term benefits (both on reproductive potential and quality of life) have gained little attention so far.

A recent study has reported that cancer survivors are more likely to use emergency contraception than their peers (Medica *et al.*, 2018), opening a debate on the best way to empower them with fertility awareness and enhancing the need for a multidisciplinary approach that includes the fertility specialist also during oncologic follow-up (Nahata and Quinn, 2018). Women who are not (or not yet) wishing for a pregnancy could benefit from a long-term follow-up for managing the gynecological adverse effects of anticancer therapies, counselling on contraception or menopause, or evaluation of their post-treatment ovarian reserve and reproductive potential. Moreover, data about the real gonadotoxicity of most therapies, especially the newest targeted agents, and the probability of premature ovarian insufficiency (POI) are still incomplete (Lambertini *et al.*, 2016). Indeed, not all women who have cryopreserved will need to use their frozen gametes or embryos to obtain a pregnancy, but they could still need the specialist consultation for various reproductive and fertility issues. A proper follow-up at an oncofertility unit would also allow the collection of data about the gonadotoxicity of the new targeted agents, an issue that will become even more important in coming years.

In this context, it is of great relevance to understand what are patients' long-term requests from the reproductive medicine specialists. This study aims at better defining these needs by evaluating the reasons for return to follow-up visits at an oncofertility unit.

Materials and Methods

Study design and participants

This is a retrospective analysis of prospectively collected data from oncofertility consultations at a single oncofertility unit. The previous studies using this data received ethical approval (CERLiguria no. 032REG2013). Eligible women for this study were newly diagnosed post-menarche cancer patients under the age of 40 years, who underwent a pre-treatment consultation between January 2012 and June 2017. Since follow-up visits are the main focus of this study, women deceased before having the chance to return were excluded, as were women with severe psychiatric disorders. All patients signed a written agreement form for the use of their data for clinical research.

Oncofertility unit

This study was conducted in a centre located within an assisted reproduction service, in a gynecological department of a university tertiary hospital. The centre has an active collaboration in terms of patients' referral from both oncologists and hematologists of all cancer services within the same hospital and the survivorship clinic of the nearby pediatric hospital as well as several other smaller regional institutions. Pre-therapy consultations and follow-up visits are performed by gynecologists with expertise in reproductive endocrinology and infertility, specifically trained through internal educational sessions and multidisciplinary discussions of clinical cases (disease management team meetings). Psychological support is available for all patients on request.

Study procedures

For each patient, demographic and clinical data were recorded at her first access, along with information about ovarian reserve, the type of fertility preservation procedure proposed, and acceptance or reasons for refusal. The possibility of scheduling follow-up visits was offered to all patients, regardless the patient choice on fertility preservation techniques. The women were free to decide when and why to return to the fertility specialist; a fast-track booking system specific for these visits simplified the process. Information regarding the reason for the follow-up visit was also reported.

Study objectives and statistical analysis

The primary objective was to investigate the reasons for young cancer patients returning to a follow-up visit at an oncofertility unit after a first consultation performed before starting anticancer therapies. In addition, potential predictive factors for return to follow-up were explored.

Table I Characteristics of study participants: total sample and only patients who returned for a follow-up visit.

	All patients ($n = 154$) n (%)	Patients who returned for a follow-up visit ($n = 74$) n (%)
Age at diagnosis, years	31 [26–36]	31 [27–35]
Presence of a partner at diagnosis	57.7% (89/154)	68.9% (51/74)
Nulliparity at diagnosis	85.7% (132/154)	79.8% (59/74)
Type of malignancy		
Breast cancer	47.4% (73/154)	51.3% (38/74)
Hematologic cancer	31.8% (49/154)	28.4% (21/74)
Others	20.8% (33/154)	20.3% (15/74)
High gonadotoxic therapy	22.1% (34/154)	22.9% (17/74)
Ovarian reserve at diagnosis		
Anti-Mullerian hormone—AMH (ng/ml)	1.77 [1.06–3.29]	1.77 [1.16–3.66]
Antral follicular count—AFC (n)	12 [8–18.5]	12 [8–17]
Fertility preservation procedures *		
Oocyte cryopreservation *	22.7% (35/154)	25.7% (19/74)
Ovarian tissue cryopreservation *	11.7% (18/154)	12.2% (9/74)
Ovarian transposition *	5.8% (9/154)	4.05% (3/74)
Cryopreservation procedures not proposed	25.3% (39/154)	20.2% (15/74)
GnRH agonist **	66.8% (103/154).	67.6% (50/74)

Continuous data expressed as median [1st–3rd quartile]; categorical data expressed as percentage.
*Some patients ($n = 5$) have done more than one procedure.
**Of these 103 patients, 44 had used only GnRH agonists and 59 also had a cryopreservation procedure.

Continuous data are expressed as median with first and third quartiles, and categorical data are expressed as absolute number and percentage. Reasons for the first follow-up visit among subgroups of patients affected by different malignancies were compared through chi square test. Logistic regression was used to explore the presence of potential predictive factors for return to follow-up. A P-value <0.05 was considered statistically significant. Statistical analysis was carried out with the software R, version 3.5.2.

Results

Characteristics of study participants

We enrolled in the study a total of 154 women. Demographic and clinical characteristics of the patients are reported in Table I. The two most common malignancies were breast ($n = 73$, 47.4%) and hematological ($n = 49$, 31.8%) cancers. Half of the patients ($n = 89$, 57.7%) reported to be in a stable relationship at the time of the first visit and the majority of them ($n = 132$, 85.7%) were childless. On note, only a minority ($n = 34$, 22.1%) received treatments with proven high risk of gonadotoxicity (i.e. conditioning for bone marrow transplantation). The other patients underwent therapies with low-to-moderate or unknown gonadotoxicity risk.

Cryopreservation procedures

In total, 57 patients (37% of the total cohort) underwent a fertility preservation procedure. Oocyte cryopreservation was performed for 35 patients (22.7%), ovarian tissue cryopreservation for 18 patients (11.7%), and ovarian transposition for 9 patients (5.8%). Five patients did more than one procedure. A total of 103 patients (66.8%) used monthly injection of gonadotropin-releasing hormone (GnRH) analogs during chemotherapy for gonadal protection. Three patients who refused a cryopreservation procedure before a low gonadotoxicity first-line therapy underwent ovarian tissue cryopreservation before a second-line therapy of higher gonadotoxic potential.

Of the total sample, 39 women (25.3%) did not undergo any fertility preservation procedures for medical reasons. Of the remaining 115 patients, 61 (53%) refused any cryopreservation procedure as a personal choice. Patients flow and uptake of fertility preservation procedures, including reasons for non-eligibility and refusal, are shown in Fig. 1.

Return to the oncofertility unit for a follow-up visit

Almost half of the total cohort of patients ($n = 74$, 48%) returned at least once to the oncofertility unit for a follow-up visit.

Half of the patients returned to the oncofertility unit for the first time after a mean time of 3.92 months (±2.44 months) following the end of the anticancer therapies (51.3%), 40.5% returned during treatment, and 8.1% returned after having experienced a relapse.

Regarding the reasons for follow-up visits, only eight patients (10.8%) returned actively desiring a pregnancy; among these, three had a spontaneous pregnancy, four started an ovarian stimulation for ART, and one used her oocytes cryopreserved at the time of diagnosis.

The main reasons for the first visit were evaluation of the gonadotoxic effects on the reproductive potential (39.2%) and management

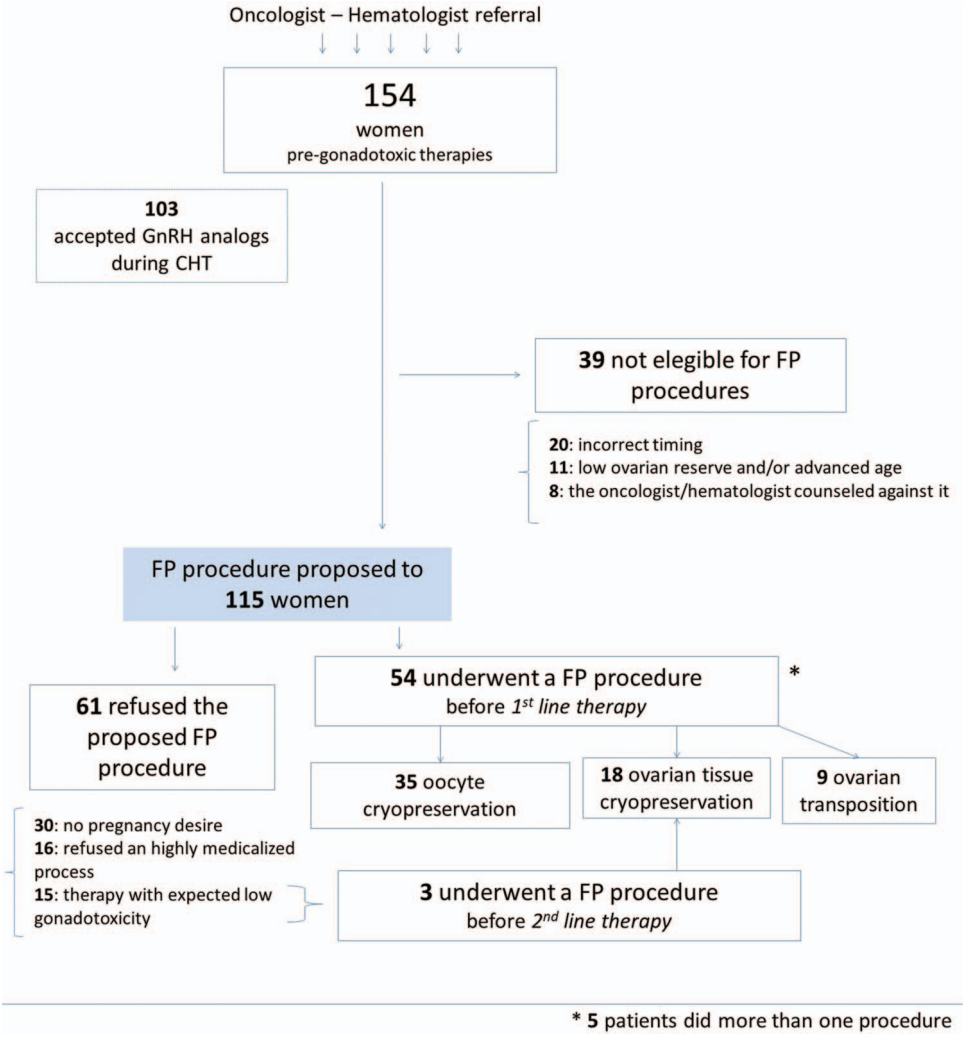

Figure 1 Patients flow and uptake of fertility preservation procedures.
FP = fertility preservation; GnRH analogs = gonadotropin-releasing hormone analogs; CHT = chemotherapy.

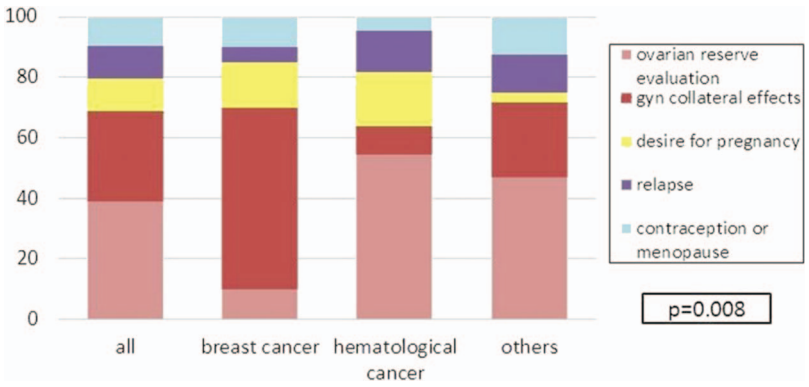

Figure 2 Reason for a follow-up visit, overall and according to type of malignancy.
Data is expressed as percentage and compared with chi square test. Statistically significant difference ($P = 0.001$). gyn = gynaecological.

Table 2 Predictive factors of return to the oncofertility unit for a follow-up visit.

Potential predictive factor	Odds ratio [95% C.I.]	*P*-value
Being in a relationship at diagnosis	2.29 [0.94–4.65]	NS
Being childless at diagnosis	0.61 [0.21–1.76]	NS
Pre-treatment AMH <1 ng/ml	1.19 [0.49–2.91]	NS
Breast or hematological cancer	1.53 [0.66–3.54]	NS
High gonadotoxicity of therapies	1.22 [0.53–2-80]	NS
Prior access to a cryopreservation procedure	1.13 [0.55–2.30]	NS

of treatment-related gynecological adverse effects (29.7%). Patients required consultations also for counselling about contraception (4.1%) and menopausal symptoms (5.4%). Moreover, eight patients (10.8%) returned before starting a new and more gonadotoxic therapy for a relapse of their malignancy.

Figure 2 shows the reasons for follow-up visits according to type of malignancy (breast, hematological, others). The most common reason for follow-up was management of gynecological adverse effects for breast cancer patients and evaluation of reproductive potential for women with hematological malignancies.

Table 2 examines possible predictive factors of return to the oncofertility unit for a follow-up visit. Being childless, having a low ovarian reserve at diagnosis, exposure to high gonadotoxic therapies, type of malignancy, and a prior cryopreservation procedure were not shown to be predictors of return to a follow-up visit.

Discussion

While the role of the oncofertility unit in counselling on infertility risk and fertility preservation options is universally endorsed (Oktay *et al.*, 2018; Peccatori *et al.*, 2013; International Society for Fertility Preservation, 2012; Ethics Committee of American Society for Reproductive Medicine, 2013; ASRM, 2013b; Lambertini *et al.*, 2017a), less attention is paid to its function in cancer survivors (Nahata and Quinn, 2018; Anazodo *et al.*, 2019), except when patients require the access to ART procedures and the use of cryopreserved material. To our knowledge, this is the first study reporting rates of and reasons for oncofertility follow-up in young cancer patients, with the aim to better define a potential broader role of the oncofertility unit in their management.

For young cancer patients, fertility is undoubtedly a relevant issue with the majority of them showing concerns about the potential risk of treatment-related POI and infertility after appropriate oncofertility counselling (Lambertini *et al.*, 2018; Ruddy *et al.*, 2014). Undoubtedly, the timely communication between oncologists, hematologists, and reproductive medical specialists enables a personalised counselling in which ovarian reserve can be evaluated, the gonadotoxicity of therapies can be discussed, and a fertility preservation procedure can be proposed whenever appropriate (Vu *et al.*, 2017; Von Wolff *et al.*, 2015). In our experience, oncologists and hematologists give general information about gonadotoxic risks of treatments and the possibility of undergoing fertility preservation procedures, proposing a dedicated oncofertility consultation with the reproductive medical specialists to all women who desire more information regardless of their attitude towards cryopreservation procedures. The acceptance rate of cryopreservation procedures in our study seems low (49.6%); however, notably, the majority of these patients chose not to undergo a procedure as a conscious personal decision after complete counselling (either because they completed their family planning or due to the low gonadotoxicity of the proposed therapies). Nevertheless, also patients who have completed their family planning and have no desire for other children may be worried about the adverse effects associated with POI development and desire reliable information about their ovarian reserve (Vu *et al.*, 2017; Lambertini *et al.*, 2018). It is plausible that this interest remains strong also during and after the end of anticancer therapies. As suggested by our results, the ideal path of a young woman at the oncofertility unit starts at cancer diagnosis but continues during and after gonadotoxic therapies, and this is not only limited to pregnancy desire or use of cryopreserved material (Fig. 3).

Various evidence in the literature shows how the needs of cancer survivors may be not yet met by gynecologists in an optimal way over the long term (Schover, 2018; Anderson *et al.*, 2018). Reduced sexual quality of life (Schover, 2018) and reduced chance of pregnancy (Anderson *et al.*, 2018) were observed among patients with all cancer types, including those who underwent surgery without gonadotoxic therapies. Gynecological adverse effects of therapies and treatment-related loss of fertility clearly play a relevant role in these results, but other psychological and social factors (i.e. concern about recurrence, reproductive issues not adequately addressed, or other health issues) may contribute (Howard-Anderson *et al.*, 2012; Schmidt *et al.*, 2016).

During gonadotoxic therapies, early gynecological adverse effects are a significant issue. In the literature, cancer patients, especially those treated with chemotherapy, report low rates of overall sexual satisfaction and less arousal and pleasure, and these problems are not always adequately addressed (Condorelli *et al.*, 2019; Schover, 2018; Dominick *et al.*, 2015). This requires specific expertise, especially in women who had hormone sensitive cancers and, therefore, limited treatment options (American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice and Farrell, 2016). Coherently, 29.7% of patients returned to have a follow-up visit for treatment-related issues (i.e. vaginal dryness or other menopausal symptoms). This was the main reason for the return of women with breast cancer, who are usually subjected to treatments of low-to-moderate gonadotoxicity risk, followed by 5 to 10 years of adjuvant endocrine therapy for hormone-sensitive cancers, which is associated with significant side effects.

Deeply linked to this issue, and pivotal in the restoration of a satisfactory sexual life, patients need a safe and reliable contraception. Indeed, in the literature, data suggest that they are less likely to receive adequate contraception counselling, with rates up to 56% of survivors reporting no family planning counselling at all (Castro–Sanchez *et al.*, 2018). Additionally, they are less likely to be satisfied and compliant with the prescribed method (Blouet *et al.*, 2019) and more likely to wrongly assume they are infertile and to face unwanted pregnancies (Medica *et al.*, 2018; Hadnott *et al.*, 2019). Information on contraception during chemotherapy, along with information on fertility preservation, is part of our pre-therapy counselling. Usually, oral combined contraceptives or a vaginal ring is suggested to patients without hormone-sensitive malignancies; in all other cases, barrier

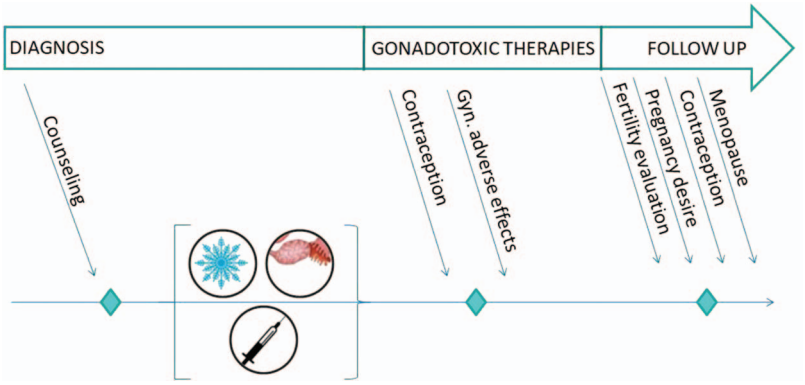

Figure 3 Proposed path of young cancer patients at an oncofertility unit. gyn = gynaecological.

contraception or copper intra-uterine device is proposed. In this study, we reported that 4.1% of visits are exclusively for contraception counselling; this seems low, but, since we discuss the topic at every visit, this percentage represents only the patients who are not satisfied with the current method and who have requested an additional consultation to re-discuss it. More data are needed to improve the counselling of young cancer patients on this regard.

An oncofertility unit, in our model, should manage patients over the long term, providing education to raise fertility awareness, to obtain the best possible sexual quality of life, to discuss the timing of a potential pregnancy and best pathway to achieve it, or to provide reliable contraception and gynecological care (including preventive measures). Also in women who develop POI, the role of the reproductive specialist is crucial for the management of hormonal therapy, if not contraindicated, or specific therapies for specific adverse effects (e.g. sexual health, bone health) (in collaboration with endocrinologists) and cardiovascular evaluation (with cardiologists). Indeed, a long-term model of care enables a punctual and dynamic evaluation of reproductive potential and gonadotoxic damage of treatments at multiple time points, with the double aim of empowering the patient with reliable information on her ovarian reserve and to better understand the real damage to fertility of anticancer therapies, on which we still have little information, especially for the new targeted agents (Lambertini *et al.*, 2016). Surveys among gynecologists without specific expertise in reproductive endocrinology and infertility show a generally low level of specific knowledge and sometimes even the inability to correctly interpret and contextualise hormonal levels assays in an infertile woman (Revelli *et al.*, 2015). Fertility evaluation post gonadotoxic therapies is even harder for many reasons. First of all, traditional markers may be less useful after prior exposure to gonadotoxic therapies. In fact, anti-Mullerian hormone (AMH) levels are reported to be particularly low right after chemotherapy, also in women with residual fertility (Freour *et al.*, 2017; Anderson *et al.*, 2017). In addition, a regular menstrual cycle is not always an indicator of fertility restoration while, on the other hand, amenorrhea could be only temporary (Partridge *et al.*, 2010; Decanter *et al.*, 2018).

The majority of women in our cohort returned for the first follow-up visit for a reproductive potential evaluation (39.2%), and this included patients who opted out of fertility preservation techniques when offered, proving how the interest remains strong also after treatments. This was the main reason for follow-up in women with hematological malignancies, who are subjected to therapies that span from low gonadotoxicity (i.e. first line therapy for lymphoma with ABVD (adriamycin/bleomycin/vinblastine/dacarbazine) regimen protocol) to high gonadotoxicity (i.e. conditioning for bone marrow transplantation). Hence, both patients who chose not to undergo a cryopreservation procedure because of the low gonadotoxicity of the therapies and patients who underwent high gonadotoxicity therapies (independently of whether or not having had a cryopreservation procedure) are both expected to desire a reproductive potential evaluation. There is no consensus on when and how fertility investigation after cancer therapy is predictive of future fertility. We usually perform ovarian reserve evaluation at each visit (i.e. AMH levels, antral follicular count, presence of menses), informing the patient that their results, even hypergonadotropic amenorrhea, are not conclusive of residual fertility. In our opinion, since ovarian reserve evaluation cannot be done in a single visit and most of the markers are dynamic and vary during and after the end of gonadotoxic therapies, a proper follow-up at the oncofertility unit is the key for both patient's empowerment and advancement in scientific knowledge.

In patients who desire a pregnancy, fertility awareness enables them to better define when and how to safely attempt a pregnancy after cancer. The likelihood of pregnancy in women who previously had a malignancy is reduced by ~38% compared to the general population (Anderson *et al.*, 2018), in all age groups at diagnosis and in all malignancies. The advent of new therapies and the consequently reduced morbidity and mortality, as well fertility preservation options, has increase the incidence of pregnancy after cancer in the last 10 years (Anderson *et al.*, 2018), but there is still a long way to go. The collaboration between woman, reproductive medical specialist, and oncologist or hematologist can minimise the risks and maximise the chances of success, since there is actually no perfect time to try for a pregnancy after cancer (Lambertini *et al.*, 2017b), and only the combination of data about the malignancy and the woman-specific reproductive potential can lead to a pregnancy attempt, which is both safe and effective. Thanks to the information acquired with a long-term model of care, the patient can be adequately counselled on the best way to achieve a pregnancy (i.e. trying to conceive spontaneously, using

reproductive technologies or her cryopreserved material, or using an oocyte donor and/or a gestational carrier). In our cohort, only 10.8% of women returned to follow-up for the first time actively desiring a pregnancy. Many other, included the ones who already returned for other reasons, may try to conceive in the future, since our follow-up is relatively short.

In conclusion, our experience suggests the needs of cancer patients in accessing the oncofertility unit for counselling and care even when they do not want (or cannot yet have) a pregnancy. Fertility and gynecological health care after cancer are a result of many complex variables and require tailored and long-term evaluation. Continuity of care, as requested by patients in our experience, could ultimately increase the reproductive potential, empowering women to make conscious choices on when and how to attempt a pregnancy, if desired, but also on effective contraception and, in general, on improving their quality of life. Although our sample is small and reflects the experience of a single centre, it contributes in describing the heterogeneous needs of young cancer patients before, during and after gonadotoxic therapies, advocating for a broader role of an oncofertility unit. With the advancement of research in this setting, the role of the oncofertility unit is destined to change from acute 'rescue therapy' to long-term counselling and care that can and must be offered, including to women for whom a fertility preservation procedure is not indicated or not requested.

Authors' roles

C.M. contributed to the study design and data collection, performed the statistical analysis, and drafted the manuscript. P.S. and M.L. contributed to the study design and patient management and critically revised the article. F.S. contributed to the clinical management of patients and data collection. V.R. critically revised the study protocol and the manuscript. P.A. designed the study, was responsible of clinical management of patients and general supervision, and critically revised the article. All authors read, revised, and approved the final version of the manuscript.

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Conflict of interest

M.L. served as a consultant for Teva and received honoraria from Theramex outside the submitted work. The other authors declare no conflict of interest.

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