

## ORIGINAL ARTICLE

# Preliminary results of a counselling programme for fertility preservation in female cancer patients: The experience of the GEMME DORMIENTI network

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## Abstract

**Objective:** To describe a population of patients referred for fertility preservation (FP), how to efficiently provide FP care, and how FP care changed over time.

**Methods:** This longitudinal observational study enrolled 281 female cancer patients referred between 2013 and 2016 to the non-profit organisation Gemme Dormienti ONLUS (GD) for FP care. All patients underwent the same battery of instrumental and laboratory diagnostic tests. GnRHa therapy was started at least seven days before CTh treatment.

**Results:** From 2013 to 2016, we observed a progressive increase in the number of patients referred for FP care. Out of 251 eligible patients, 135 patients were treated with GnRHa only, and 72 patients underwent GnRHa therapy and cryopreservation. The median time from GD referral to oocyte and ovarian tissue cryopreservation was 11 and 5 days respectively. Tissue cryopreservation requests increased during our study period (from four cases in 2013 to 17 cases in 2016). During follow-up,  $17\beta$ -estradiol and FSH levels were significantly increased ( $p < .0001$ ), and AMH levels were significantly decreased ( $p < .0001$ ).

**Conclusion:** The rapid increase in the number of patients who requested FP care and in the complexity of FP procedures overtime reflects the need to improve quality of life for cancer patients.

## KEYWORDS

cancer, counselling, fertility preservation, GnRHa, oocyte cryopreservation, ovarian tissue cryopreservation

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## 1 | INTRODUCTION

The remarkable prolongation of survival seen in younger cancer patients in the past decades (Siegel, Miller, & Jemal, 2017) has shed light on the long-term side effects of anti-cancer therapies. Among these, temporary or permanent fertility impairment (Gracia et al., 2012; Stensheim, Cvancarova, Møller, & Fosså, 2011) raises concerns for reproductive-age patients facing gonadotoxic therapies, causing psychological distress and possibly affecting treatment decision (Lawson et al., 2014; Partridge et al., 2004; Ruddy et al., 2014). Hence, fertility preservation (FP) care has become paramount in this complex setting. Several strategies are currently available, including ovarian suppression through gonadotropin-releasing hormone agonists (GnRHa) and cryopreservation of oocytes as well as ovarian tissue. The use of GnRHa during chemotherapy (CTh) is an attractive option to preserve both ovarian function and fertility, with the advantage of avoiding delays in cancer treatment (Lambertini, Ginsburg, & Partridge, 2015). Compelling evidence supports the benefit yielded by GnRHa administration in cancer patients in terms of reduced risk of CTh-induced premature ovarian failure (POF) (Del Mastro et al., 2011, 2014; Lambertini et al., 2014; Lambertini, Ceppi, et al., 2015; Moore et al., 2015) and increased pregnancy rates (Del Mastro et al., 2011; Lambertini, Ceppi, et al., 2015; Matteo Lambertini et al., 2014, 2017; Moore et al., 2015; Wong, O'Neill, Walsh, & Smith, 2013), with no negative impact on prognosis (Lambertini, Ceppi, et al., 2015). Despite the efficacy of this option in some cancer types, GnRHa remains controversial (Behringer et al., 2012; Blumenfeld, Zur, & Dann, 2015; Demeestere et al., 2016; Tavares, Senra, Talim, & Reis, 2016). While a protective effect has been demonstrated in breast cancer patients (Del Mastro et al., 2011, Del Mastro et al., 2014, Blumenfeld et al., 2015, Blumenfeld & Evron, 2016), more studies are needed to confirm the protective role of GnRHa in patients with other types of cancer (Demeestere et al., 2016, reviewed in Lambertini, Horicks, Mastro, Partridge, & Demeestere, 2019). The Italian Association of Medical Oncology (AIOM) has recently issued a strong positive

recommendation to adopt the use of GnRHa for both ovarian function and FP in cancer patients (Lambertini et al., 2017). We believe that the use of GnRHa is useful in preserving fertility regardless of the type of tumour (Blumenfeld & Evron, 2016; Garrido-Oyarzun & Castelo-Branco, 2016; Lambertini et al., 2019).

Oocyte cryopreservation is now considered a standard FP option (Practice Committee of American Society for Reproductive Medicine, 2013). However, it requires controlled ovarian stimulation (COS), which may delay CTh and affect the prognosis of patients with hormone-responsive tumours (Lambertini et al., 2016). To overcome this problem, alternative approaches have been developed, either to avoid COS (i.e. cryopreservation of immature oocytes or of oocytes matured in vitro [Cao & Chian, 2009; Oktay et al., 2008]) or to start it at any time (i.e. random start protocol that requires  $\geq 2$  weeks of treatment [Cakmak & Rosen, 2013]).

Ovarian tissue cryopreservation has been proven to be effective for the recovery of ovarian function, but remains an experimental procedure (Lambertini et al., 2016; Practice Committee of American Society for Reproductive Medicine, 2013). Tissue cryopreservation may be performed at any time during the menstrual cycle without COS and is currently the only option for pre-pubertal girls facing gonadotoxic therapies. Moreover, it is suitable for patients who cannot delay CTh initiation, who have already received a few cycles of low gonadotoxic risk CTh or have contraindications to COS. However, tissue cryopreservation is generally suitable for women aged  $< 35$  years, and the success of the procedure depends on ovarian reserve (Matteo Lambertini et al., 2016). Currently, in vitro maturation techniques are under investigation to prevent the risk of malignant cell re-implantation associated with this technique (Blumenfeld, 2016; Salama, Isachenko, Isachenko, Rahimi, & Mallmann, 2016).

Several international guidelines recommend physicians to promptly and comprehensively inform patients facing gonadotoxic treatment about the risks of fertility impairment and the possibility of FP and to support them throughout the decision-making process (AIOM, 2016; ISFP Practice Committee et al., 2012; Loren et al., 2013;

Peccatori et al., 2013; Practice Committee of American Society for Reproductive Medicine, 2013). Both physicians and patients have acknowledged the importance of offering oncofertility counselling and having multidisciplinary teams (MDT) that establish individualised approaches based on the patient's characteristics. Despite the reported physical and psychological benefits and improved quality of life (QoL) in patients undergoing FP care (Deshpande, Braun, & Meyer, 2015; Razzano et al., 2014), FP counselling and procedures are not routinely implemented as part of patient care (Diesch et al., 2017).

Nonetheless, the increasing rate of referrals to FP centres and of FP procedures performed reflects the efforts to improve patient care in this complex and rapidly evolving setting (Sigismondi et al., 2015; Vu, Llarena, Estevez, Moravek, & Jeruss, 2017).

The Gemme Dormienti (GD) ONLUS is an Italian non-profit association established in 2011 by experienced physicians willing to provide free professional support for women coping with gonadotoxic treatment, due to cancer or other conditions, and severe impairment of QoL. By supporting these patients throughout the process of FP, GD aims at restoring their ovarian function and increasing their chances of pregnancy.

In this study, we characterise the population of patients referred to GD for FP care, how these patients were managed, and how FP care changed over time.

## 2 | METHODS

### 2.1 | Study design

This is an observational, single-centre study documenting the strategy of FP care given to female cancer patients of reproductive age, referred to GD between 01/01/2013 and 31/12/2016.

We collected data on the main demographic and clinical characteristics of cancer patients (the ones affected by other pathologic conditions were excluded), past and planned therapies, and FP strategy adopted. A sample size calculation was not carried out because we performed an observational study in which all eligible patients who were referred to our centre during the study period were enrolled.

### 2.2 | Patient population

Patients were included if post-pubertal, aged <45 years and if they had a diagnosis of cancer requiring gonadotoxic treatment. All of them were eligible for treatment with GnRHa. Patients were eligible for cryopreservation if aged ≤38 years, and if they had not previously received high-risk CTh or HSCT. Exclusion criteria were a poor prognosis *quoad vitam* and histologically or cytologically confirmed ovarian metastases.

All patients referred to GD provided signed informed consent. For patients aged <18, the consent was signed by the legal tutor. Study approval was obtained by the Ethics Committee of IDI IRCCS (Istituto Dermatologico dell'Immacolata—Istituto di Ricovero e Cura a

Carattere Scientifico) Prot. n. 45/CE/2017. The study was conducted in accordance with the Declaration of Helsinki.

### 2.3 | Oncofertility programme

The oncofertility programme developed by GD aims to provide patients with comprehensive FP counselling and screening of ovarian function, supporting them in the decision-making process, and taking appropriate measures to avoid delays in cancer treatment. The GD's programme relies on a network of oncologists, oncohaematologists and paediatric centres from hospitals and universities across Italy. Upon diagnosis of cancer, healthcare providers can schedule an appointment at GD within 24–48 hr through a dedicated phone number to ensure rapid access to the FP programme. During the medical appointment at GD, a gynaecological examination is carried out, medical (physiological, family, gynaecological and cancer) history is taken, and the treatment plan is carefully revised.

Through a centralised laboratory that manages to provide results within 6 hr, the following assessments are carried out: hormonal profile (follicle-stimulating hormone [FSH], luteinizing hormone [LH], 17β-estradiol [17βe], progesterone, prolactin, thyroid-stimulating hormone [TSH], and anti-müllerian hormone [AMH]), Pap-test, pelvic ultrasound scan with antral follicle count (AFC) and endometrial thickness. These exams are the standard of care outlined by AIOM guidelines for FP in cancer patients. The strength of the FP programme developed by GD is to complete the whole assessment on the same day: due to time constraints, blood samples for hormonal profiling are collected randomly.

Patients >18 years were requested to fill a questionnaire to assess their psychological status and motivation to pursue FP. They were offered counselling throughout the entire treatment period and during follow-up if needed. Patients were given follow-up examinations 1, 6, 12, 24 and 36 months after completion of CTh. Further follow-up appointments were scheduled according to the patients' availability.

### 2.4 | Fertility preservation techniques

The options adopted by GD to preserve fertility are chemoprevention with GnRHa and/or cryopreservation of oocytes and/or ovarian tissue.

All post-pubertal patients <45 years received GnRHa, which is reimbursed by the Italian healthcare system since July 2016, regardless of the type of tumour. The decision for cryopreservation was made based on patient's age, treatment plan and ovarian reserve at baseline. Eligible patients willing to undergo the procedure were referred to public centres of excellence in Italy. According to the programme, GnRHa therapy was started at least 7 days before CTh treatment, to avoid chemotherapy during the expected ovarian flare-up that follows GnRHa administration. The time frame between the first GD examination, FP procedures and the start of chemotherapy was of 7–10 days in the case of ovarian tissue preservation, and 3 weeks

Characteristics	All	GnRHa	GnRHa + Cryo		No FP
	N = 251	N = 135	Oocytes N = 31	Tissue N = 41	N = 44
Age, years	31 (3–44)	31 (18–44)	30 (17–38)	24 (3–33)	38 (14–44)
Parity (na = 1)					
0	190 (76)	94 (69.6)	27 (90)	37 (90.2)	32 (72.7)
1	35 (14)	25 (18.5)	3 (10)	2 (4.9)	5 (11.4)
2–5	25 (10)	16 (11.9)	0 (0)	2 (4.9)	7 (15.9)
Education (na = 40)					
Secondary school	25 (11.8)	14 (12.1)	1 (3.8)	6 (17.6)	4 (11.4)
High school	110 (52.1)	65 (56)	9 (34.6)	20 (58.8)	16 (45.7)
Degree	76 (36)	37 (31.9)	16 (61.5)	8 (23.5)	15 (42.9)
Occupation (na = 44)					
Housekeeper/ unemployed	9 (4.3)	3 (2.6)	1 (3.7)	2 (6.5)	3 (8.8)
Student	55 (26.6)	27 (23.3)	8 (29.6)	15 (48.4)	6 (17.6)
Craft workers and others	39 (18.8)	24 (20.7)	5 (18.5)	4 (12.9)	6 (17.6)
Professionals	104 (50.2)	62 (53.4)	13 (48.1)	10 (32.3)	19 (55.9)
Cancer type					
HL	118 (47)	65 (48.1)	15 (48.4)	26 (63.4)	12 (27.3)
NHL	53 (21.1)	32 (23.7)	5 (16.1)	5 (12.2)	11 (25)
Breast cancer	37 (14.7)	19 (14.1)	8 (25.8)	2 (4.9)	8 (18.2)
Leukaemia	21 (8.4)	13 (9.6)	2 (6.5)	2 (4.9)	4 (9.1)
Other solid/hema- tol. malignancies <sup>§</sup>	22 (8.8)	6 (4.4)	1 (3.2)	6 (14.6)	9 (20.5)
First-line therapy					
RT (na = 2)	101 (21.4)	57 (21.1)	12 (21.8)	16 (19.3)	16 (24.6)
CTh (na = 12)	227 (48)	129 (47.8)	24 (43.6)	39 (47)	35 (53.8)
ABVD	116 (24.5)	63 (23.3)	15 (27.3)	26 (31.3)	12 (18.5)
CHOP	29 (6.1)	21 (7.8)	4 (7.3)	2 (2.4)	2 (3.1)

Note: Data are expressed as median (range) or frequency (n [%]).

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; Cryo, cryopreservation; CTh, chemotherapy; GD, Gemme Dormienti Onlus; GnRHa, gonadotropin-releasing hormone agonist; HL, Hodgkin lymphoma; na, not available; NHL, non-Hodgkin lymphoma; RT, radiotherapy.

**TABLE 1** Demographic and clinical characteristics of female cancer patients deemed as adequate for fertility preservation, at the time of first referral to Gemme Dormienti

in the case of oocyte pick-up, due to the need for COS (Oktay et al., 2008). Usually, two weeks are enough to perform COS. RANDOM START protocols—which allow stimulation to start immediately, regardless of the phase of the cycle in which the patient is—have been proposed to avoid long waiting times and treatment delays (Allen et al., 2018; Moravek et al., 2018). If the patient is referred immediately to GD's for FP (while she is doing the tests for the diagnosis and staging of her disease, as per protocol), the delay is minimal and of no influence on disease outcome (Allen et al., 2018 and Moravek et al., 2018). For patients affected by Hodgkin's lymphoma, tissue cryopreservation laparoscopy could be performed after the second ABVD cycle if an early restaging showed a poor response or, in case

of relapse, before the salvage therapy, generally consisting in high-dose chemotherapy (HD-CTh) and autologous stem cell transplantation (ASCT).

## 2.5 | Statistical analysis

Patients' characteristics were summarised by means of frequency (*n*) and percentage (%) for categorical variables or by means of *n* min *q*1 median *q*3 max for continuous variables.

Boxplots were used to show AMH, FSH and 17Be2 values during the follow-up visits. Differences among groups were evaluated in univariate analysis by means of non-parametric tests (chi-squared

and Fisher's exact test in case of categorical variables or response rate, Mann–Whitney and Kruskal–Wallis test in case of continuous variables). Confidence intervals were estimated at 95% level, and all tests were two-sided, accepting  $p < .05$  as indicating a statistically significant difference. All analyses were performed using the SAS system (version 9.4) and R software.

### 3 | RESULTS

#### 3.1 | Patient population and FP

From 2013 to 2016, we screened a group of 281 female patients. Out of these, 30 (10.7%) patients were affected by non-neoplastic chronic conditions (multiple sclerosis, rheumatoid arthritis, Behçet's syndrome, thalassaemia major, Myelodysplastic syndrome, aplastic anaemia, among others), did not fulfil the inclusion criteria and were therefore excluded from the study. The remaining 251 (89.3%) were cancer patients, aged <45 years, and deemed eligible for FP with the following diagnosis: Hodgkin lymphoma (HL,  $n = 118$ , 47%), non-Hodgkin lymphoma (NHL,  $n = 53$ , 26.6%), breast cancer ( $n = 37$ , 14.7%), leukaemia ( $n = 21$ , 8.4%), other solid and haematologic malignancies ( $n = 22$ , 8.8%).

The main demographic and clinical characteristics of the population are shown in Table 1 according to the fertility strategies adopted. At the time of the first referral to GD, the median age of all patients was 31 years (range: 3–44). In the three FP groups (GnRHa, GnRHa and oocyte cryopreservation, and GnRHa and ovarian tissue cryopreservation), median age was 31 years (range: 18–44), 30 years (17–38) and 24 years (range: 3–33) respectively. The median age of patients was significantly higher in the group not undergoing FP than in the other groups (38 years, range: 14–44,  $p < .0001$ ).

In the GnRHa group, ovarian suppression was achieved by administration of leuprorelin acetate in 112 patients (83.0%) and triptorelin in 18 (13.3%). Five patients (3.7%) chose to continue taking the contraceptive pill they were already on to avoid GnRHa adverse effects.

Among these, patients were considered eligible for cryopreservation if they were aged  $\leq 38$  years, had a good prognosis *quoad vitam*, no sign of ovarian metastases and no previous administration of high-risk CTh or autologous HSCT (haematologic stem cell transplant).

The chemoprevention approach alone was employed in 135 patients (65.2%), whereas 41 (19.8%) underwent GnRHa treatment and ovarian tissue cryopreservation. Thirty-one patients (15.0%) were treated with GnRHa and performed oocyte cryopreservation (Table 1). One patient included in the GnRHa, and tissue cryopreservation group underwent also oocyte cryopreservation. In the GnRHa only group ( $n = 135$ ), cryopreservation was not performed in 12 patients (8.89%) because they were over the age limit (>38 years old). In the remaining 123 age-eligible patients, cryopreservation was not performed for several reasons: personal choice ( $n = 42$ , 31.11%), referral after high-risk CTh or HSCT ( $n = 39$ , 28.89%), lack of cryopreservation indication as they had to undergo low-risk CTh

( $n = 21$ , 15.56%), not being able to postpone CTh ( $n = 17$ , 12.59%), and surgical contraindication due to medical conditions ( $n = 4$ , 2.96%).

A total of 24 patients were treated between 2013 and 2016 with oocyte stimulation (mean oocytes taken: 9 [1–33]). Out of 24 patients, 2 (8.3%) had an adverse event (ovarian hyperstimulation syndrome). In both cases, the adverse event was resolved according to the guidelines with case-specific therapies.

Most patients were nulliparous in all groups. In the oocyte or tissue cryopreservation groups, 64 patients (88.9%) were nulliparous, and 8 (11.1%) had already given birth. In the GnRHa only group, nulliparous and parous patients were 94 (69.6%) and 41 (30.4%) respectively ( $p = .002$ ).

Most patients were high school graduates (56.0% in the GnRHa, 34.6% in the GnRHa and oocyte cryopreservation, 58.8% in the GnRHa and tissue cryopreservation, and 45.7% in the no FP group) or college graduates (31.9%, 61.5%, 23.5% and 42.9% respectively). Patients had intellectual or technical jobs (53.4%, 48.1%, 32.3% and 55.9% respectively), unskilled jobs (20.7%, 18.5%, 12.9% and 17.6% respectively) or were students (23.3%, 29.6%, 48.4% and 17.6% respectively).

Hodgkin lymphoma (HL) accounted for most cases in all groups [65 patients (48.1%) in the GnRHa only group, 15 (48.4%) in the GnRHa and oocyte group, and 26 (63.4%) in the GnRHa and tissue cryopreservation group], followed by NHL (32 [23.7%], 5 [16.1%] and 5 [12.2%] respectively) and breast cancer (9 [14.1%], 8 [25.8%] and 2 [4.9%]). As first-line treatment, nearly 40% of patients ( $n = 101$ ) in all groups underwent radiotherapy and almost all received CTh. Forty-five patients received HSCT.

The median time from GD referral to oocyte retrieval was 11 days (range: 1–35). The median time for laparoscopic surgery for ovarian tissue cryopreservation was five days (range: 1–22). Five patients underwent tissue cryopreservation laparoscopy after low-risk chemotherapy and before HSCT.

Patients were given follow-up appointments 1, 6, 12, 24 and 36 months after completion of CTh for gynaecological examination, review of clinical history, pelvic ultrasound scan with antral follicular count and endometrial thickness, and blood tests for hormonal profiling.

AMH, FSH and 17 $\beta$ e levels at baseline and during the follow-up visits are presented in Table 2 and showed in Figure 1.

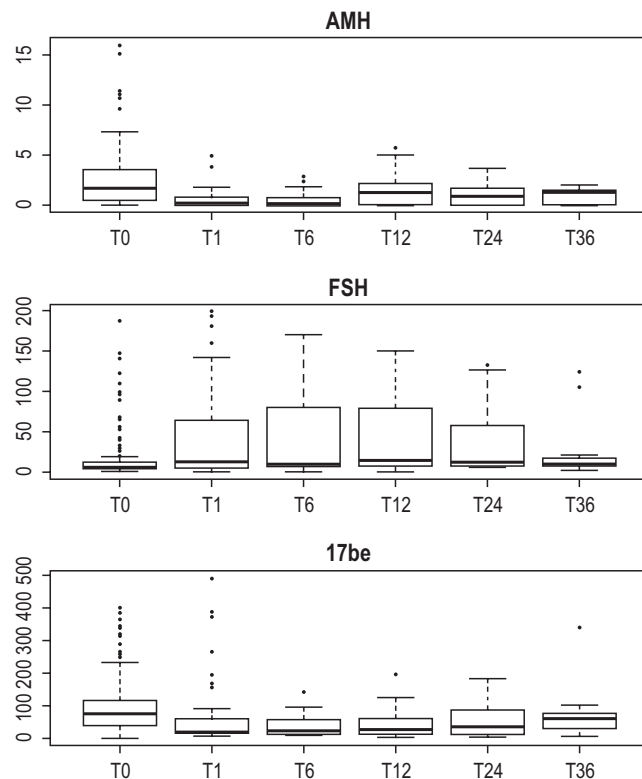
Cross-sectional results are shown in Table 2 for the follicular, ovulation and luteal phase; no statistical association was observed between baseline AMH levels and menstrual cycle phase ( $p = .25$ ), while median FSH and 17  $\beta$ e levels were statistically significantly higher in the follicular phase for FSH ( $p < .0001$ ) and in ovulation phase for 17  $\beta$ e ( $p < .0001$ ).

Seven patients had post-treatment pregnancies, all of which occurred spontaneously. Of these, three patients were treated with ABVD for HL, one with RCHOP for NHL, one with EC and Taxol for breast cancer, one with just tamoxifen for breast cancer (suspended after two years of treatment to achieve a pregnancy). One patient was not treated with CTh but underwent an ovariectomy

**TABLE 2** AMH, FSH and 17BE levels at baseline (overall and according to the menstrual cycle phase) and during the follow-up visits

	T0 (n = 219) median (range)	T1 (n = 64) median (range)	T6 (n = 27) median (range)	T12 (n = 21) median (range)	T24 (n = 18) median (range)	T36 (n = 9) median (range)
<b>AMH</b>						
Overall	1.7 (0.0–16.0)	0.1 (0–5)	0.1 (0–2.8)	1.21 (0–5.8)	0.92 (0–3.7)	1.5 (0.02–1.9)
Follicular	2.1 (0.1–16.0)					
Ovulation	2.9 (0.5–7.1)					
Luteal	1.9 (0.0–5.5)					
<b>FSH</b>						
Overall	5.7 (0.1–147)	8.1 (0.3–194.93)	8.9 (0.24–171.1)	12.4 (0.6–115.3)	12.8 (4.3–132.8)	10.5 (4.2–123.9)
Follicular	6.6 (1.6–23.9)					
Ovulation	4.3 (0.1–14.0)					
Luteal	4.1 (0.7–52.6)					
<b>17be</b>						
Overall	76.0 (0.01–401)	22.2 (5–488)	24.5 (11–145)	25 (3.8–125)	28.5 (5–149)	53.5 (5–74)
Follicular	50.5 (0.02–323.0)					
Ovulation	132 (11–348)					
Luteal	104 (1.5–384)					

Abbreviations: AMH, anti-müllerian hormone; FSH, follicle-stimulating hormone.

**FIGURE 1** Boxplot of anti-müllerian hormone, follicle-stimulating hormone and 17BE levels at baseline and during the follow-up visits

for a Granulosa cell neoplasm. Two of them performed ovarian tissue cryopreservation but did not re-implant the tissue, whereas all the patients who underwent CTh were co-treated with GnRHs. We

registered six live births with healthy babies and one first-trimester miscarriage.

## 4 | DISCUSSION

FP care (GnRHs and/or cryopreservation of ovarian tissue and oocytes) must be personalised and specific for each patient. Ovarian tissue cryopreservation is still considered an experimental procedure but presents several advantages, namely the possibility to start chemotherapy immediately after surgery and a wider range of eligible candidates, which includes pre-pubertal patients. The number of pregnancies after autotransplantation of cryopreserved ovarian tissue is growing fast (Meirow et al., 2016; Van der Ven et al., 2016). It was recently reported that, worldwide, almost 100 children have been conceived following transplantation of frozen-thawed ovarian tissue (89 successful births and nine ongoing pregnancies at the time of manuscript writing) (Donnez & Dolmans, 2017; Jensen et al., 2017). Ovarian tissue cryopreservation is aimed not only at preserving fertility in cancer survivors but also ovarian function, which has been compromised by cancer therapies. Although a useful strategy, ovarian tissue cryopreservation presents some limitations, namely the concern of reseeding cancer cells during ovarian transplantation. The risk of re-introducing cancer cells after re-implantation depends on the type of tumour and ranges from low (<0.2%) to high (>11%). Indeed, while ovarian involvement is rare in some tumours, systemic cancers, such as aggressive leukaemia, pose a higher risk (Oktay, 2001). However, recent studies have shown that it is possible to safely re-implant ovarian tissue in cancer patients, including leukaemia survivors, if appropriate precautions are taken and preliminary

examinations on the tissue performed (Ben-Aharon et al., 2016; Meirou et al., 2016).

Oocyte cryopreservation is considered a standard FP option but is not suitable for pre-pubertal girls and, due to the need for COS, cannot be used when therapy must be urgently started. In addition, some precautions must be taken in the case of patients with hormone-sensitive tumours.

All eligible patients enrolled in our study were offered at least one FP option. Patients who underwent neither oocyte nor ovarian tissue cryopreservation were significantly older than the others.

Most patients were nulliparous in all groups, and a significantly higher number of these patients chose to undergo cryopreservation of oocytes or tissue, whereas most women who had given birth before were treated with GnRHa only ( $p = .002$ ).

Hodgkin lymphoma (HL) accounted for most cases in all groups, followed by NHL and breast cancer due to the high rate of long-term survival of patients with HL and a more intensive collaboration between GD and the Lymphoma Lazio District.

Blood test monitoring was used as a first evaluation of post-chemotherapy hormonal activity. At follow-up (1, 6, 12, 24 and 36 months after the completion of CTh treatment),  $17\beta$ -estradiol and FSH levels were significantly increased ( $p < .0001$ ), while a statistically significant decrease was observed for AMH levels ( $p < .0001$ ). As blood tests at baseline were performed randomly, cross-sectional results were given for the follicular, ovulatory and luteal phase; no statistical association was observed between baseline AMH levels and menstrual cycle phase ( $p = .25$ ) (Fréour, Barrière, & Masson, 2017; Iwase, Nakamura, Nakahara, Goto, & Kikkawa, 2015), while median FSH and  $17\beta$ e levels were statistically significantly higher in the follicular phase for FSH ( $p < .0001$ ) and in the ovulation phase for  $17\beta$ e ( $p < .0001$ ).

The incidence rate of pregnancies and live births from GD's FP programme is still not available for most patients due to the duration of the follow-up, since an average observation of 3–5 years is required for the diseases considered in the present paper.

Recent studies highlighted the importance of FP counselling (Deshpande et al., 2015), presence of a psychologist (Razzano et al., 2014) and improved education for healthcare teams (Diesch et al., 2017) in reducing dissatisfaction concerning fertility, and improving physical/psychological QoL.

In our experience, most patients benefited from the GD's FP programme since they underwent procedures that contributed to fertility preservation and future pregnancies. Cryopreservation was not performed in a subgroup of eligible patients, as almost 1/3 of these patients refused the procedure for personal choice (Jones et al., 2017). For this reason, GD asked all patients >18 years to fill out four validated psychological questionnaires at baseline and during follow-up and offered psychological support during and after treatment, both for patients undergoing FP treatments and those who refused treatment. The analysis of this psychological survey will be the object of further investigations.

Our preliminary results are supported by several studies showing that patients who receive specialised counselling about reproductive

loss and pursue fertility preservation have a better quality of life. Women suffering from gynaecological tumours may also be eligible for fertility-sparing surgery that can preserve their reproductive potential (Chiofalo et al., 2017; Vitale, Rossetti, Tropea, Biondi, & Laganà, 2017). Therefore, it is important to provide complete information about fertility preservation options and to transform patients into active decision-makers in the treatment process (Laganà, Rosa, Rapisarda, Platania, & Vitale, 2017; Letourneau et al., 2012; Vitale, Rosa, Rapisarda, & Laganà, 2018).

GD's FP programme is free, effective and standardised according to international guidelines (Dalle et al., 2017; Font-Gonzalez et al., 2016; Lewin et al., 2017). Because of the lack of a systematic FP programme in most regions in Italy, GD's network aims to promote a valid model for FP counselling, assessment and treatment that could improve the NHS's FP care currently offered to young cancer patients (Quinn et al., 2016). We believe that our effort put in informing oncologists, haematologists, paediatricians and other specialists on FP care resulted in an active network, and a well-designed FP programme that is able to provide a high-quality service to young patients in need of better FP care.

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## CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

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